A PORTABLE MONITOR FOR THE MEASUREMENT OF PERIODIC LIMB MOVEMENTS IN RESTLESS LEGS SYNDROME: VALIDITY AND RELIABILITY

by

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Abstract

**Purpose:** A key objective feature in Restless Legs Syndrome (RLS) is the presence of Periodic Limb Movements (PLMs). The gold standard for documenting PLMs is through polysomnogram (PSG), an overnight sleep study in a sleep laboratory, which is expensive and often inaccessible. This work explored the ability of a portable sleep monitor (PM) to reliably record surface EMG signals, to reliably record limb movements overnight in comparison with PSG, and examined intra- and inter-rater reliability for scoring the PM recordings.

**Methods:** The PM’s surface EMG channel was tested against a standard EMG amplifier by recording bilateral tibialis anterior muscle activity in five healthy participants. It was also tested for recording PLMs simultaneously with polysomnography at Kingston General Hospital with 40 participants referred for screening of sleep disorders. PLMs were scored using standard criteria according to the American Academy of Sleep Medicine Scoring Manual (2007)

**Analyses:** Comparison between the two methods of surface EMG recording was through counts of muscle activity bursts. Comparison of overnight PLM counts was through t-test, Pearson’s r, Intraclass Correlation Coefficient (ICC) and Bland-Altman plots. Intra-rater reliability and inter-rater reliability between two analysts was examined by ICC.

**Results:** Examination of the PM surface EMG recordings demonstrated an exact match of muscle activity counts between the PM and standard EMG recordings. In the PSG study, mean difference between the two PLMI values was +4.8 ± 11.1, t (34) = 2.1, p = 0.04, which was statistically significant and demonstrated systematic over-reporting by the portable monitor. The two PLMI values were strongly correlated, giving a Pearson’s r = .87, p < 0.001. ICC for absolute agreement was 0.87, (95% CI, 0.76 – 0.93), p < 0.001. Bland-Altman analysis gave 95% limits of agreement between the two PLM Indices as +27.9 (95% CI +33.0 to 20.2) to – 19.3 (95%CI -10.6 to -23.4).

**Conclusions:** These data suggest there may be sufficient agreement between PLMI collected by PM and polysomnography to support the use of the PM for measuring PLMs. Further testing should address test retest reliability and examine the performance of the PM in a wider patient population.
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# Table of Contents

Abstract ........................................................................................................................................ ii

Acknowledgements ..................................................................................................................... iii

List of Abbreviations .................................................................................................................. x

Chapter 1 Introduction .................................................................................................................. 1

1.1 Restless Legs Syndrome ....................................................................................................... 1

1.2 Objective Measures of Restless Legs Syndrome Status ..................................................... 3

1.3 Research Purpose .................................................................................................................. 4

Chapter 2 Literature Review ........................................................................................................ 5

2.1 Pathophysiology of Restless Legs Syndrome ....................................................................... 5

  2.1.1 Cortical Spinal Dysfunction ............................................................................................ 5

  2.1.2 Circadian Rhythm ............................................................................................................ 8

  2.1.3 Endogenous Opioid System Dysfunction ....................................................................... 9

  2.1.4 Dopamine Regulation ..................................................................................................... 10

  2.1.5 Iron regulation ................................................................................................................. 11

  2.1.6 Vascular Dysfunction .................................................................................................... 12

  2.1.7 Summary ..................................................................................................................... 13

2.2 Treatment ............................................................................................................................. 13

  2.2.1 Pharmacological treatment ............................................................................................ 13

  2.2.2 Non-pharmacological treatment .................................................................................... 14

2.3 Diagnosis .............................................................................................................................. 16

  2.3.1 Essential Criteria ............................................................................................................ 17

  2.3.2 Periodic Limb Movement Index (PLMI) ....................................................................... 17

  2.3.3 Scoring Limb Movements in Sleep ............................................................................... 19

  2.3.4 Reliability of scoring PSG recordings ........................................................................... 21

  2.3.5 Periodic Limb Movement Disorder ............................................................................... 22

  2.3.6 RLS-diagnostic index (RLS-DI) .................................................................................... 22

  2.3.7 Accessibility of sleep studies ......................................................................................... 23

  2.3.8 Suggested Immobilization Test ..................................................................................... 24
Chapter 3 ........................................................................................................... 32

Validity of the Medibyte for recording surface EMG .............................. 32

3.1 Study 1 Research Question ...................................................................... 32

3.2 Introduction & Rationale .......................................................................... 32

3.2.1 Study Objective ....................................................................................... 33

3.3 Methods .................................................................................................... 34

3.3.1 Study design ........................................................................................... 34

3.3.2 Instrumentation ....................................................................................... 34

3.3.2.1 Medibyte® Portable Monitor .............................................................. 34

3.3.2.2 Bortec AMT-8® EMG System ........................................................... 36

3.3.3 Participants ............................................................................................ 38

3.3.4 Procedures ............................................................................................. 38

3.3.5 Data Analysis ........................................................................................ 41

3.4 Results ...................................................................................................... 42

3.5 Discussion .................................................................................................. 43

3.5.1 Key Findings .......................................................................................... 43

3.5.2 Surface EMG collection ......................................................................... 43

3.5.3 Periodic Limb Movement Measurement .............................................. 45

3.5.4 Study Limitations .................................................................................. 46

3.6 Conclusion .................................................................................................. 46

Chapter 4 .......................................................................................................... 48

Reliability and Validity of the Medibyte for recording limb movements in comparison with PSG ................................................................. 48

4.1 Study 2 Research Questions ..................................................................... 48

4.2 Introduction & Rationale .......................................................................... 48

4.2.1 Restless Legs Syndrome ....................................................................... 48

4.2.2 The Braebon Medibyte as a potential PLM recording device .............. 49
4.2.3 Reliability of scoring PSG recordings .......................................................... 50
4.2.3 Study Objectives ......................................................................................... 51

4.3 Methods ....................................................................................................... 52
4.3.1 Study Design ........................................................................................... 52
4.3.2 Instrumentation ......................................................................................... 52
  4.3.2.1 Polysomnography ............................................................................... 52
  4.3.2.2 Medibyte® Portable Monitor .............................................................. 55
4.3.4 Participants ............................................................................................... 59
4.3.5 Procedures ................................................................................................ 59
  4.3.5.1 Periodic Limb Movement Index (PLMI) Scoring .................................. 62
  4.3.5.2 Intra- & Inter-rater Reliability of scoring PLMI derived from Medibyte® ............................................................................................................. 68
4.3.6 Data Analysis ............................................................................................ 68

4.4 Results .......................................................................................................... 69
4.4.1 Validity of PLMI determined by Medibyte® versus by PSG ....................... 71
  4.4.1.1 Correlation of PLMI values .................................................................. 72
  4.4.1.2 Full night versus split night studies .................................................... 74
  4.4.1.3 Bland-Altman agreement analysis ...................................................... 75
4.4.2 Intra-rater reliability .................................................................................. 76
4.4.3 Inter-rater reliability .................................................................................. 76

4.5 Discussion ..................................................................................................... 77
4.5.1 Key Findings ............................................................................................. 77
4.5.2 PLMI Over-reporting by the Medibyte® .................................................... 78
4.5.4 Absolute agreement .................................................................................. 79
4.5.5 Potential Sources of Error .......................................................................... 80
  4.5.5.1 Arousal information on the portable monitor recording ......................... 80
  4.5.5.2 Lack of real time monitoring ............................................................... 81
  4.5.5.3 Splitting of nasal flow signal .................................................................. 81
  4.5.5.4 EMG electrode placement .................................................................... 82
4.5.6 Efficacy/Utility of the MB ....................................................................... 82
4.5.7 Study Limitations & Future Directions ..................................................... 83

4.6 Conclusion .................................................................................................... 84

Chapter 5 .......................................................................................................... 85
Discussion .................................................................................................................. 85

5.1 Key Findings of the Research ............................................................................. 85
5.2 Muscle Activity Onset Detection ....................................................................... 85
5.3 PLMI as an Outcome Measure ........................................................................... 86
5.4 RLS-Diagnostic Index (RLS-DI) ....................................................................... 86
5.5 Minimal clinical difference ................................................................................. 87
5.6 Suggested Immobility Test (SIT) ....................................................................... 89
5.7 Portable Sleep Monitors versus Actigraphy for Measuring PLMs ....................... 90
5.8 Future Directions ............................................................................................... 91
5.9 Conclusions and Recommendations .................................................................. 92

References ................................................................................................................... 93

7.1 Definitions of Breathing Events During Sleep ...................................................... 107
7.2 International Restless Legs Syndrome Study Group Severity Scale .................... 108
7.3 Scoring of the IRLSSG Severity Scale ................................................................ 111
7.4 RLS-DI (Diagnostic Index) ................................................................................ 114
7.5 Study 1 Letter of Information and Consent ......................................................... 116
7.6 Study 1 Ethics Approval ..................................................................................... 119
7.7 Study 2 Letter of Information and Consent ......................................................... 120
7.8 Study 2 Ethics Approval ..................................................................................... 123
List of Figures

Figure 2-1a One Hz sine wave .................................................................27
Figure 2-1b One Hz sine wave sampled at 2 Hz.....................................29
Figure 2-1c One Hz sine wave sampled at 3Hz......................................28
Figure 2-1d One Hz sine wave sampled at 1.5 Hz.................................28
Figure 2-1e One Hz sine wave recreated when sampled at 1.5 Hz.........28
Figure 3-1 Medibyte® dimensions: 2.5 x 2.25 x 0.75 inches (66 x 60 x 19mm) ..................35
Figure 3-2 Medibyte® portable monitor set up for OSA screening...........34
Figure 3-3 Bortec AMT-8® Amplifier.......................................................35
Figure 3-4 Bortec® APE500R pre-amplifier and leads..........................36
Figure 3-5 Equipment set up for surface EMG collection for Study 1........38
Figure 3-6 Splitter connections allowing simultaneous collection of EMG by Medibyte® and Bortec AMT-8® with one set of electrodes.................................................................38
Figure 3-7 Bortec® recording – EMG only..............................................39
Figure 3-8 Medibyte® recording. Leg muscle activity is recorded on the top tracing .............40
Figure 4-1 Polysomnogram instrumentation with exception of the nasal cannula (http://www.talkaboutsleep.com/sleep-basics/viewasleepstudy.htm, retrieved May14, 2012).....53
Figure 4-2 Diagram showing location of the EEG electrodes in a PSG set up. Note Cz – reference electrode (KGH Sleep Laboratory education materials, 2012).................................54
Figure 4-3 Medibyte® portable monitor for home screening of Obstructive Sleep Apnea (http://www.braebon.com/products/medibyte/index.php, retrieved June 8, 2011, 11:17am)....55
Figure 4-4 Medibyte® portable monitor set up for Sleep Apnea screening........59
Figure 4-5 Medibyte® portable monitor PLM set up................................60
Figure 4-6 120 second screenshot of a PSG tracing (PLM03)...............65
Figure 4-7 120 sec Medibyte® recording.................................................66
Figure 4-8 Screenshot of a 30 second section of a Pursuit sleep study ................67
Figure 4-9 Correlation of PLMI from Medibyte® with PSG PLMI. Vertical lines represent cut-off values for RLS diagnosis(15) and PLMD diagnosis (25)..................................................74
Figure 4-10 Bland-Altman plot.................................................................76
List of Tables

Table 3-1 Summary of EMG data acquisition specifications with each system.......................... 38
Table 3-2 Participant demographics .................................................................................. 42
Table 3-3 Comparison of contraction counts........................................................................ 43
Table 4-1 Comparison of PSG and Medibyte® channels/features; Medibyte can record EKG OR
EMG, not both at the same time. ....................................................................................... 57
Table 4-2 Surface EMG acquisition specifications for both EMG recording systems .......... 58
Table 4-3 Summary of patient demographics; N= number, SD = standard deviation .......... 66
Table 4-4 PLMI values from PSG and from Medibyte® .................................................... 73
Table 4-5 Summary of results of statistical analysis of reliability of the PLMI by Medibyte® vs.
PLMI by PSG; PLMI = Periodic Limb Movement Index, NS = not significant ................. 77
List of Abbreviations

IRLSSG – International Restless Legs Syndrome Study Group

IRLS – International Restless Legs Syndrome Study Group Severity Scale

LM(s) – Limb Movement(s)

OSA – Obstructive Sleep Apnea

PAM-RL® - brand name of a portable monitor for the assessment of restless legs

PLM(s) – Periodic Limb Movement(s)

PLMD – Periodic Limb Movement Disorder

PLMI – Periodic Limb Movement Index

PM – Portable Monitor

PSG - Polysomnography

RLS – Restless Legs Syndrome

RLS-DI – RLS Diagnostic Instrument

SIT – Suggested Immobilization Test
Chapter 1

Introduction

1.1 Restless Legs Syndrome

Restless Legs Syndrome is a chronic condition that causes significant discomfort and distress to those who have it. It is defined as “a neurological disorder characterized principally by leg parathesiae (unpleasant sensations) and motor restlessness (urges to move)” (Michaud, Paquet, Desautels, Poirier, & Montplaisir, 2002). The incidence of Restless Legs Syndrome (RLS) noted in the general population varies, but a recent review of the epidemiological literature including 47 studies from North America, Europe, Japan and Turkey found that the prevalence of RLS depends in part on how it is evaluated. Studies based on the essential diagnostic criteria yield a prevalence of 5% - 8.8% in the general population (Ohayon & Roth, 2002; Ohayon, O’Hara & Vitiello, 2012). The prevalence is approximately twice as high in women and increases with increasing age in North America and Europe but not in Asian countries (Ohayon & Roth, 2002; Ohayon et al., 2012). Typical age of onset is in the 40s or 50s though RLS can occur at any age (Ohayon & Roth, 2002; Ohayon et al., 2012).

While complaints of unpleasant sensations in the legs and urges to move might seem trivial, this condition can cause significant negative impact on quality of life. Quality of life evaluations of people with RLS show what might seem a surprisingly significant degree of impairment (Allen, 2007b). People with moderate to severe RLS may have their sleep patterns completely disrupted leading to major loss of energy and ability to enjoy life. Results of the RLS Epidemiology, Symptoms and Treatment (REST) Study (Allen, et al., 2005) demonstrated that individuals with RLS scored significantly lower than the general population in all eight areas of the Short Form-36 Health Survey. In fact their scores were comparable to those of people with
other chronic diseases such as individuals with diabetes and depression. In the Energy/Vitality domain of the SF-36, for example, individuals with RLS had a mean score significantly lower (p < 0.05) than age and sex adjusted norms for the United States general population. “RLS may be a thief of sleep, but it is even more a destroyer of the quality of life.” (Allen, 2007b, p 202)

The causes of RLS are yet to be fully established but in greater than 50% of cases there is a familial history (Allen, et al., 2003). Research to date suggests that the symptoms may be “generated centrally within the brain by local iron deficiency and dopaminergic dysfunction” (Ekbom & Ulfberg, 2009 p. 419). In particular, studies have shown that there can be low iron stores in the brain (Allen & Early, 2007) and a decrease in the brain neurotransmitter, dopamine (Connor, et al., 2009), but it is not known how these deficiencies cause the signs and symptoms of RLS. Medications are the typical mode of treatment, with iron supplementation also being of some benefit (Trenkwalder, et al., 2008). Medications that boost dopamine production, while often very successful initially, can have the complication of actually worsening the symptoms at other times of day, and over time the treatment effect of medications can diminish (Trenkwalder, Hogl & Winkelman, 2009). Additionally, there are side effects to these treatments that can make them difficult to tolerate (Trenkwalder, Hogl & Winkelman, 2009).

Over the past two decades there has been increasing interest in exploring new, and improving existing treatment options for people with RLS. Intervention studies have examined many drug therapies (Garcia-Borreguero, et al., 2007; Jama, et al., 2009; Oertel, et al., 2010); a few have studied non-pharmacological treatments (Aukerman, et al., 2006; Esteves, DeMello, Pradella-Hallinan & Tufik, 2008; Lettieri & Eliasson, 2008; Sakkas, et al., 2008). Outcome measures in these studies are typically changes in subjective measures, usually using the International Restless Legs Syndrome Study Group (IRLSSG) RLS severity rating scale, a validated patient completed instrument (International Restless Legs Syndrome Study Group,
Some trials have attempted to quantify change objectively using limb movement measurement in combination with subjective measures or on its own (Garcia-Borreguero et al., 2007, Aukerman et al., 2006, Jama et al., 2009).

1.2 Objective Measures of Restless Legs Syndrome Status

A key supportive feature of the diagnosis and severity of RLS is the presence of periodic limb movements (PLMs). These are involuntary rhythmic movements of the legs that can occur during sleep or waking (Allen et al., 2003). The standard method to measure PLMs is via polysomnography (PSG) or overnight sleep study to give an index of number of PLMs per hour of recording. This requires an overnight stay at a sleep laboratory (Allen et al., 2003) where patients are outfitted with multiple recording sensors to collect electroencephalographic information, oximetry, nasal/oral flow pressure, respiratory effort, and surface electromyography (EMG) signals. For research purposes, requiring several PSG studies of every participant in an intervention study is impractical, inconvenient for participants and would likely negatively impact recruitment. In clinical practice, there is typically a long waiting list for in centre sleep studies and they are not universally available (Rotenberg, George, Sullivan & Wong, 2010).

In 2003, the National Institutes of Health Restless Legs Syndrome Workshop called for the development of portable devices to enhance the use of PLM measurement as an objective outcome to support the diagnosis of RLS (Allen et al., 2003). The ability to reliably document objective measures of RLS status would both increase the ease of diagnosis, and the quantification of objective change due to treatment, and ultimately improve the management of RLS (Allen et al., 2003). Portable sleep monitors that also measure muscle activity potentially provide more accessible methods of measuring PLMs that could be used by the patient/participant overnight in their own home. One such device recently validated for home screening of moderate
to severe Obstructive Sleep Apnea (OSA) is the Braebon Medibyte® portable home sleep monitor (Driver et al., 2011).

1.3 Research Purpose

The purpose of this research was to explore the validity and reliability of the Medibyte® portable monitor as a tool for capturing surface EMG, and as a method for measuring PLMs and determining a PLM Index (PLMs/hour) in overnight sleep studies in comparison with PSG. Intra and inter-rater reliability for obtaining a PLM Index (PLMI) from overnight portable monitor recordings was also determined.
Chapter 2

Literature Review

2.1 Pathophysiology of Restless Legs Syndrome

Several key features of RLS have led researchers to postulate a variety of potential pathways for the causation of the symptoms and signs of RLS. The consistent occurrence of the symptoms in the evening and through the night has prompted examination of links with circadian rhythm (Trenkwalder, et al., 1999; Bara-Jimenez, Aksu, Graham, Sato & Hallett, 2000; Kerr, Bentley, Anderson & Mckinon 2010; Gundez, Adatepe, Kiziltan, Karadeniz, & Uysal, 2012). Clinical observations of RLS in individuals with peripheral vascular disease have sparked a vascular theory (Ekbom & Ulfberg, 2009). Manifestation of RLS in association with other conditions (peripheral neuropathy, Parkinson’s disease, spinal cord injury) has led to research into possible neurophysiological mechanisms (Rye, 2004). This area has received the most concentrated attention and study. Additionally, there has been much debate over whether the main mechanism underlying RLS is peripheral or central in origin (Paulus et al., 2007). The occurrence of secondary forms of RLS with other conditions that are associated with iron deficiency suggests a role for iron in the RLS pathway (Allen & Earley, 2007). This review will provide information and evidence on key areas of research in the field of RLS pathophysiology.

2.1.1 Cortical Spinal Dysfunction

There are numerous case reports of RLS associated with spinal pathology, even with complete paraplegia (Hartmann, Pfister, & Pfadenhauer, 1999). PLMs are noted to be a very stereotypical involuntary movement akin to the Babinski reflex or the spinal cord flexor reflex (Bara-Jiminez et al., 2000), which suggests the hypothesis that decreased supraspinal or cortical inhibition of descending motor pathways could be a trigger of PLMs. In a study with ten people
with primary RLS and ten age and gender matched controls, Bara-Jimenez et al (2000) demonstrated that the flexor reflex was disinhibited in individuals with RLS compared to controls during both sleep and wakefulness. They measured levels of stimulus intensity (measured as multiples of individual sensory threshold) required to stimulate a flexor response in both states. Control participants demonstrated marked levels of inhibition of the flexor response during sleep versus wake (p < 0.001) which RLS participants did not (p = 0.98). During wake RLS participants also showed a significantly lower threshold than controls to the late component of the flexor response (p < 0.001) (Bara-Jimenez et al., 2000). The authors concluded that these results demonstrate increases in spinal cord excitability in people with RLS, especially in sleep.

In an examination of spinal cord excitability using patellar reflex testing, another study found that while there were circadian fluctuations in patellar reflex parameters (quadriiceps electromyographic (EMG) amplitude, maximum knee angular velocity and displacement) in people with RLS (n=11) compared with controls (n=9), the individuals with RLS tended to be hypo-reflexic in the evening (Kerr et al., 2010). EMG amplitude was decreased during reflex testing in the RLS group during the evening (median value = 0.25 millivolts) in comparison with the morning (median value = 0.6 millivolts, p = 0.0078) and also in comparison to the control group (morning median value = 0.75 millivolts; evening median value = 0.7 millivolts, p = 0.04). Additionally, knee angular displacement was significantly less in the evening (median 138.4°; interquartile range =132.9–146.2) in the group with RLS versus their morning measurements (median =150.5°; interquartile range =138.6–158.9)(p = 0.018) (Kerr et al., 2010). These researchers found their results did not support spinal hyper-excitability as mechanism for PLMs.

Cortical mechanisms implicated in RLS have been explored using Transcranial Magnetic Stimulation (TMS). This technique allows non-invasive study of cortical excitability and inhibition and involves discharging a magnetic pulse over the scalp (Reid, 2003). This magnetic
pulse induces electrical depolarization in the areas of the cerebral cortex underlying the pulse location, and when used over the motor cortex, results in a motor evoked potential. Surface EMG is used to record information about the muscle activity occurring during the TMS pulse. When the pulse is applied during a sustained voluntary contraction there is a temporary decrease in EMG activity, which is known as the cortical silent period (Entezari-Tahe, 1999; Reid, 2003.). This pause in EMG activity occurs due to a combination of peripheral, spinal and cortical mechanisms (Reid, 2003). Some studies have found this silent period to be significantly shorter for the tibialis anterior muscle in people with RLS. In a comparison of ten individuals with RLS and ten healthy age matched controls, Entezari et al (1999) determined the cortical silent period to be $66.8 \pm 25.6$ milliseconds versus $136 \pm 40$ milliseconds respectively (p < 0.05).

Gunduz et al (2012) compared measures of cortical activity and EMG activity during TMS in the morning and in the evening in 11 individuals with RLS and 8 age and sex matched controls. The differences in cortical silent period duration between groups did not reach statistical significance in their study. The results did demonstrate a statistically significant reduction in the active motor threshold of the first dorsal interosseus muscle of the hand in participants with RLS between the morning and evening test sessions (held on different days), which did not occur in the control participants; $28.5\pm6.2\%$ versus $40.4\pm8.4\%$, p=0.006 (Gunduz, et al., 2010). These findings support the hypothesis that there is decreased intracortical inhibition in the brains of individuals with RLS.

Unrath, Juengling, Schork & Kassubek (2007) demonstrated structural changes in the brains of people with RLS. A technique known as optimized voxel-based morphometry (VBM) was used. This process analyzes three-dimensional MRI images on the basis of volume, with a voxel defined as a volumetric pixel (Whitwell, 2009). Analysis of 63 participants with primary RLS and 40 healthy controls demonstrated areas of significant decrease (p < .005) in grey matter
volume in the primary somatosensory cortex as well as in the left primary motor region (Unrath et al., 2007). Whitwell (2009) cautions that there is great potential variability in this type of study and differences should only be considered anecdotal until procedures are more standardized.

Other recent imaging studies have shown conflicting results. A brain mapping technique known as diffusion tensor imaging that uses MRI and the physical properties of water diffusion can reveal white matter structural abnormalities (Hagmann et al., 2006). Using combined VBM and diffusion tensor imaging, Rizzo et al., (2011) demonstrated no clear structural or microstructural differences in the brains of 20 individuals with RLS versus 20 healthy individuals. Comley et al., (2012) came to similar conclusions using VBM in 8 people with RLS and 8 controls. The question of structural brain differences in people with RLS is still very much under debate.

### 2.1.2 Circadian Rhythm

Occurrence of the leg paresthesiae and PLM in RLS predominantly in the evenings suggests a circadian influence. Trenkwalder et al., (1999) explored potential circadian modulation of RLS in eight participants who were monitored for PLMs, RLS symptoms, and core body temperature over the course of two days and three nights, the last night being sleep deprived. Patterns of PLMs and symptoms closely followed the same circadian fluctuations. In all participants with RLS, on all nights, peak PLMI occurred between 12:00 AM and 1:AM. The lowest PLMI values were between the hours of 9:00AM and 2:00PM. The low PLMI values were all significantly different from the peak PLMI values (p < 0.05) (Trenkwalder et al., 1999). The authors observed that this pattern closely matches daily fluctuations in body temperature; with most PLMs occurring as the body temperature was falling. Body temperature is lowest around five in the morning (Weinert & Waterhouse, 2007). This suggests that some disorder or
disruption of body temperature regulation may be associated with the symptoms of RLS and PLMs.

Several studies already cited regarding cortico-spinal mechanisms have shown circadian variations in a variety of measures that differ between individuals with RLS and healthy individuals (Bara-Jimenez et al., 2000; Gundez et al., 2012; Kerr et al., 2010,). Clearly, there is strong evidence of a circadian pattern to the manifestations and pathophysiology of RLS.

2.1.3 Endogenous Opioid System Dysfunction

Opioid agents have been used successfully to treat the pain and discomfort symptoms of RLS (Trenkwalder et al., 2008). This has led to investigations of the role of the endogenous opioid system in the pathophysiology of RLS (von Spiczak et al., 2005; Walters, Ondo, Zhu & Le, 2009). Using PET scanning after injection of a radioactive opioid agonist, investigators were able to compare binding at opioid receptor sites in the brains of 15 individuals with RLS and 12 age and gender matched control participants (von Spiczak et al., 2005). Analysis of the PET images revealed no overall differences in opioid receptor binding between individuals with RLS and those without. However significant negative correlations were found between receptor binding and severity of RLS in specific areas of the brain, including the medial thalamus, the anterior cingulate gyrus, and right and left amygdala (p < 0.05) (von Spiczak et al., 2005). The investigators suggested that there may be decreased availability of opioid receptors in people with severe RLS due to increased receptor binding in those individuals. Decrease in available opioid receptors could be reflective of increased release of endogenous opioids in their systems in response to RLS symptoms (von Spiczak, 2005).

Walters et al (2009) conducted a pilot study examining the brains of five individuals with RLS postmortem in comparison with five individuals without RLS. Cell numbers were counted from 10 slides per individual at the level of the thalamus and substantia nigra. Statistically
significant reductions were noted in numbers of Beta-endorphin cells (37.5%, p = .006) and Met-enkephalin positive cells (26.4%, p = .028) in brains of people with RLS compared to those without (Walters, et al., 2009). The authors conclude from their findings that endogenous opioids may be decreased in the sensory pathways of individuals with RLS in comparison with controls. Further post-mortem studies of this type using three-dimensional techniques were recommended (Walters et al., 2009)

### 2.1.4 Dopamine Regulation

Clinical experience of the marked effectiveness of dopaminergic medications in relieving signs and symptoms of RLS is strongly suggestive of dopamine system dysfunction as a cause of RLS (Montplaisir et al., 1986; in Comella, 2002). This has prompted research examining possible links (Earley, Hyland & Allen, 2006; Oboshi et al., 2012; Connor et al., 2009). The circadian pattern of RLS signs is matched by fluctuations in dopamine levels. Central nervous system dopamine activity is lowest during evening/night hours (Sowers & Vlachakis, 1984, in Earley, Barker, Horska & Allen, 2006). Testing of cerebrospinal fluid from 30 people with RLS and 22 age/gender matched controls in the morning and later evening demonstrated significantly more 3-0-methyldopa (30MD), a metabolite of dopamine, in people with RLS at both time points (Earley, Hyland & Allen, 2006). Samples of cerebrospinal fluid drawn at 10pm averaged 12.09 ± 2.05nmol/l of 30MD for controls and 21.04 ± 3.38 for RLS, p < 0.05 (Earley, Hyland & Allen, 2006). This was also true in the morning - <10nmol/l of 30MD in controls and 31.8 ± 5.47 in RLS, p < 0.01 (Earley, Hyland & Allen, 2006). The morning and evening values in participants with RLS were not significantly different. There were no significant differences in other markers of dopamine activity in the samples.

Advanced imaging techniques developed in recent years have enabled exploration of the living brain in individuals with RLS. Using Positron Emission Tomography scans and a
dopamine (D2/3) receptor binding marker, Oboshi et al., (2012) showed significantly lower dopamine receptor binding in the nucleus accumbens and caudate regions of the brain in eight people with primary RLS when compared to age-matched controls (p < 0.05). This would imply that those receptors are already bound to dopamine. In a similar protocol, Cervenka, et al. (2006) had contrary findings, showing increased binding potential in the striatum of 16 participants with RLS versus 16 controls (2.79 ± 0.22 versus 2.61 ± 0.17, p = 0.03). Postmortem studies of the putamen and substantia nigra have examined levels of dopamine receptors (D2) from the donated brains of individuals with RLS (Connor et al., 2009). These were shown to be significantly lower in eight individuals with RLS compared to controls (p = 0.03) (Connor et al., 2009). Additionally, the levels of D2 receptors had a strong inverse relationship with RLS severity scores of the individual prior to death (r = 0.18, p = 0.02) (Connor et al., 2009) on the 40 point IRLSSG severity scale (International Restless Legs Syndrome Study Group, 2003).

2.1.5 Iron regulation

Iron also appears to play a significant role in the pathophysiology of RLS. Decreased iron levels are implicated in the most common secondary forms of RLS (Allen & Earley, 2007). Iron deficiency anemia, end-stage renal disease and pregnancy, which can all compromise iron sufficiency, are known to trigger PLMs and the symptoms of RLS (Allen & Earley, 2007). Resolution of these conditions does result in abatement of RLS (Allen & Earley, 2007). The RLS symptoms resolve with the end of pregnancy, treatment of anemia and with kidney transplantation (Allen & Early, 2007). Examination of cerebral spinal fluid (CSF) ferritin and transferrin showed altered levels in ten participants with primary RLS in comparison with ten age matched controls (Mizuno, Mihara, Miyaoka, Inagaki & Horiguchi, 2005). Levels of CSF ferritin, the major iron storage protein, reflect the amount of total iron in the brain; levels of transferrin, the main iron transport protein, indicate the need for iron in the brain (Mizuno et al., 2005).
Values of CSF ferritin were significantly lower in the individuals with RLS (4.06 ± 0.20 ng/ml) than controls (6.68 ± 0.93 ng/ml), p < 0.01 (Mizuno et al., 2005). At the same time, CSF transferrin levels were significantly higher, 2.18 ± 0.70 mg/dl versus 1.60 ± 0.39 mg/dl (p < 0.05) (Mizuno et al., 2005). Serum levels of both ferritin and transferrin were not different between the participants with RLS and the controls (Mizuno et al., 2005). These findings suggest that brain iron levels are reduced in individuals with RLS.

Magnetic Resonance Imaging (MRI) for measuring tissue iron concentration was conducted by Earley et al (2006) on the brains of participants with early onset RLS (age of onset < 45) (n = 22), late onset (n = 19) and controls (n = 39). Ten areas of the brain were examined, with a significant difference for the iron concentration in the substantia nigra between early onset RLS (4.4 ± 0.31) and controls (5.6 ± 0.31) p = 0.02 (Earley, et al., 2006). This further supports the theory that low brain iron is involved in the pathophysiology of RLS.

2.1.6 Vascular Dysfunction

Karl A. Ekbom, who was the first to thoroughly describe RLS, generated a vascular theory (1945, in Ekbom & Ulfberg, 2009). This line of thought proposed that circulatory impairment in the legs causing ischemia, and/or a buildup of toxic metabolites, stimulates the unpleasant sensations and urges to move of RLS (Jones & Derodra, 1997). This is supported by some success with treatments targeting the peripheral vascular system, for example, compression therapy to the legs (Lettieri & Eliasson, 2008) and sclerotherapy for varicose veins (Kanter, 1995).

Based on anecdotal reports of improvements in RLS symptoms in patients being treated with sequential compression therapy (SCT) for deep vein thrombosis, SCT was trialed in a small group of 10 participants with RLS over a three-month period for one hour/day at a time prior to the usual onset of their symptoms (Eliasson & Lettieri, 2007). Severity of symptoms was
established before initiating therapy and after the trial period. Participants noted significant
decreases in their symptom severity from a mean of 24 ± 6.8 to 8 ± 8.2 (p < 0.001) on the
IRLSSG severity scale (40 point scale). The same authors did follow-up research with a larger
group of 35 individuals with RLS randomly assigned to receive pneumatic compression therapy
at therapeutic (n=21) or sub-therapeutic (n=14) pressures (Lettieri & Eliasson, 2008). Severity on
the IRLSSG severity scale was 20.3 ± 5.9 in the treatment group and19.0 ± 5.2 (NS) in the sham
group. After four weeks of treatment ratings were decreased to 8.4 ± 3.4 and 14.1 ± 3.9
respectively, which was significantly different between groups (p = 0.006).

These findings provide enough evidence to prevent a vascular hypothesis from being
completely ruled out. However, given the overwhelming evidence for RLS pathophysiology to
be rooted in a dysfunction of CNS dopamine/iron regulation, a solely vascular hypothesis is not
well founded. Researchers interested in this area might do well to examine how the documented
CNS deficiencies in RLS might co-exist with peripheral vascular contributions to RLS
pathophysiology in some individuals.

2.1.7 Summary

In summary, the current state of evidence points to possibly both structural and functional
(neurophysiological) deficits in the central nervous system as the primary cause of RLS. There is
still much work to be done to fully comprehend all elements involved and synthesize the results
of the multitude of studies to give a clear picture of RLS pathophysiology.

2.2 Treatment

2.2.1 Pharmacological treatment

Currently, most treatment approaches are pharmacological and geared to treating the
symptoms of RLS only. None are completely effective.
Some of the best-studied types of medications are dopamine agents (DeMello, Esteves & Tufick, 2004; Jama et al., 2009; Montplaisir, Karrasch, Haan & Volc, 2006; Trenkwalder et al., 2008). These boost the production and/or the action of dopamine in the brain. Levodopa, a precursor to dopamine, can have immediate significant impact on the symptoms of RLS and response to this drug is almost diagnostic of RLS (Allen et al., 2003). Unfortunately, ongoing administration of levodopa runs significant risk of causing augmentation (Garcia-Borreguero et al., 2007). Augmentation is the occurrence of the RLS symptoms at other times of day (i.e. morning/afternoon) and/or the involvement of other body parts. It can occur in as many as 80% of patients treated with levodopa (Allen & Earley, 1996).

Dopamine agonist medications are also often used, including pramipexole, ropinirole and transdermal rotigotine (Trenkwalder et al., 2008). These were found to diminish symptoms and reduce PLMs in large double-blind placebo controlled trials (Jama et al., 2009; Oertel et al., 2010). They can be used long-term and do not provoke augmentation of symptoms to the same degree as levodopa (Garcia-Borreguero et al., 2007; Trenkwalder et al., 2008).

Treatment with intravenous iron supplementation can sometimes be helpful in reducing and even entirely relieving RLS symptoms temporarily, but it is not universally successful and its use carries some health risks (Allen & Earley, 2007). Other approaches are occasionally used for symptomatic relief – benzodiazepines (e.g. clonazepam) to aid in sleep, and opioid medications to give relief of the unpleasant sensations, but have not been studied to any degree (Trenkwalder et al., 2008).

### 2.2.2 Non-pharmacological treatment

Non-pharmacological approaches to treatment have also been explored with some notable success. In particular, exercise holds promise and presents a logical treatment approach given that movement ameliorates RLS symptoms. Aukerman et al (2006) were the first to examine the
impact of exercise on RLS in a randomized control trial. Their 12-week trial involved 41 participants randomized to either an exercise or control group. The exercise group participated in treadmill walking 3 times weekly and lower extremity resistance exercises while the control group did not receive any exercise intervention. Outcome measures in this study were subjective only and included the IRLSSG severity rating scale (International Restless Legs Study Group, 2003) as the primary outcome (Aukerman et al., 2006). By six weeks, the exercise group had significantly lower scores than at baseline. Symptom severity for the exercise group at baseline was 20.6 ± 6.4 (out of a possible score of 40) and for the control group was 22.5 ± 6.4 (NS) (Aukerman et al., 2006). At six weeks the severity score was 12.6 ± 4.8 in the exercise group and 20.8 ± 7.4 in the control group (p = 0.003) (Aukerman et al., 2006). Further analysis was done (MANOVAs) to examine change in symptom severity over time according to group status. The severity scores of the control group did not change significantly from week one to week twelve, whereas the exercise group showed significant change at week six [F(2,9) = 84.0, P < .001], and no further change at week twelve (Aukerman et al., 2006). The investigators concluded that these results were promising “particularly considering the numerous other advantages known to be associated with aerobic and resistance exercises” (Aukerman et al., 2006 p. 492).

Esteves et al (2008) examined the impact of exercise on periodic limb movements (PLMs) in a group of participants with a PLMI of greater than 5 /hour and sleep complaints relating to leg discomfort. Outcome measures included PLMI obtained by PSG pre and post exercise. The participants performed one bout of strenuous physical activity and then “chronic” physical activity consisting of 72 sessions of exercise on a cycle ergometer, done 3 times weekly. The PSG measures were done again after exercise sessions 1, 36, and 72. The authors found a reduced PLMI both after the acute exercise (31.0 ± 18.4 to 24.2 ± 18.7 p < 0.05) and after the 72-session program of exercise 27.21 ± 4.73 to 14.79 ± 3.69 p < 0.05) (Esteves et al., 2008).
The final study to date to examine exercise impact on RLS was conducted on a population of individuals on hemodialysis (Sakas et al., 2008). The exercise group (n=7) performed 45 minute continuous cycling 3 times weekly on a bedside cycle ergometer; the control group (n=7) received usual care. The exercise group achieved significant improvement in subjective reports of RLS severity as measured by the IRLSSG Severity Scale; total score was reduced from 26 ± 6 (out of 40) at baseline to 15 ± 9 (p = 0.02) at the end of the exercise program (Sakas et al., 2008). There was no change found in the control group. Statistically significant change did not occur until after the 16th week of exercise. It is interesting to note that significant change in RLS severity took several weeks longer to manifest than in the previous two studies. It could be theorized that this finding could relate to the population studied - hemodialysis patients - who would tend to have more co-morbidities than participants in the other exercise studies.

Based on the results of these exercise studies, it is reasonable to theorize that exercise can have positive effect on both the subjective (severity of discomfort) and objective (PLM) aspects of RLS. Further research is needed to clarify the most effective exercise type and the mechanisms of effect.

### 2.3 Diagnosis

RLS can occur as a primary idiopathic condition, usually with an onset before age 45. These individuals typically have a strong family history of RLS (Ekbom & Ulfberg, 2009). It may also occur secondarily in association with other conditions, specifically iron deficiency, pregnancy, end-stage renal disease and chronic obstructive pulmonary disease (Ekbom & Ulfberg, 2009).
2.3.1 Essential Criteria

The diagnosis of RLS relies on clinical judgment and is based substantially on subjective reports combined with supporting features. There are four essential criteria as defined by the International Restless Legs Syndrome Study Group (IRLSSG):

a) An urge to move the legs (can be arms) usually accompanied by uncomfortable and unpleasant sensation in the legs.

b) The urge to move or unpleasant sensations begin or worsen during periods of rest or inactivity such as lying or sitting.

c) The urge to move or unpleasant sensations are partially or totally relieved by movement such as walking or stretching, as least as long as the activity continues.

d) The urge to move or unpleasant sensations are worse in the evening or night than during the day or only occur in the evening or night. (Allen et al., 2003)

The unpleasant sensations are typically described as “creepy-crawly”, “jittery”, “worms moving,” “burning”, “itching bones”, “fidgets”, or “electric current”. Other supportive criteria or associated features may include disturbed sleep, periodic limb movements (PLMs) and family history of RLS (Allen et al., 2003). In individuals diagnosed with RLS, the severity of these subjective criteria can be used to monitor response to treatment using the IRLSSG Severity Scale (International Restless Legs Syndrome Study Group, 2003) (Appendix 7.3)

2.3.2 Periodic Limb Movement Index (PLMI)

PLMs typically involve involuntary rhythmic movements of the large toe and ankle (occasionally also the knee and hip), which occur during sleep or waking, especially during the evenings (Allen et al., 2003). In a small number of individuals the arms may be involved as well. When these movements occur, it is typically in a series with regular periodicity (Allen et al.,
PLMs are reported as an Index of number of PLMs per hour asleep or per hour of recording time (Allen et al., 2003).

There is a lack of consistent well-supported argument for a specific PLMI value as a benchmark in RLS assessment. Initial guidelines (1982) proposed a PLMI of greater than 5 as indicative of a PLM disorder (Coleman, 1982), but this seems to be an arbitrary value. The most relevant studies closely examining predictive/associative value of a PLMI in diagnosing RLS were conducted more than a decade ago at the Centre d’Etude du Sommeil in Montreal, Quebec (Montplaisir et al., 1998). One of the first studies to examine the discriminant power of PLMs for differentiating participants with RLS from healthy normal controls found that a PLMI (during sleep) equal or greater than 11 gave a sensitivity and specificity of 81% (Montplaisir, et al., 1998). To control somewhat for night-to-night variability in PLMs, the participants completed two consecutive nights of PSG and the higher PLMI was used in the analysis. However, this study was small (RLS=16, controls =16) and only included individuals with severe RLS who are known to have much higher numbers of PLMs (Montplaisir, et al., 1998).

A follow-up study by the same research group with a larger sample and range of RLS severity gave somewhat different results (Michaud et al., 2002b). Participants included 100 individuals with RLS and 50 healthy controls. PSG characteristics were examined during one-night sleep studies. Their results showed that a higher PLMI cut-off better differentiated their population of participants with RLS from controls; PLMI=15, sensitivity = 87%, specificity = 80%. However, this value referenced PLMs during waking through the night only, not PLMs during sleep. The PLMI during sleep only was less sensitive (78%) and specific (76%). It is not stated whether the total PLMI was analyzed for its discriminant ability. This PLMI value of 15 has been recommended in The International Classification of Disorders of Sleep-2 (2007) and the
American Academy of Sleep Medicine (AASM) Scoring Manual (2007) as a cutoff for supporting a diagnosis of RLS.

While measurement of PLMs is the only objectively quantifiable measure of RLS status, there are problems associated with its use for this purpose. There is inherent night-to-night variability of PLMs (Michaud, 2006; Montplaisir et al., 1998). Only approximately 80% of individuals with RLS experience PLMs and in those that do, PLMs do not occur on a daily basis (Allen et al., 2003). These factors affect the reproducibility of the measure and the reliability of repeated measures. Additionally, PLMs have been noted to occur in the elderly without any disruptions of sleep or other symptomatology, so are not specific to RLS (Kohnen et al., 2007, Park & Comella, 2007). Further work exploring PLM characteristics to support RLS diagnosis is ongoing (Garcia-Borreguero et al., 2011; Rummel et al., 2010)

2.3.3 Scoring Limb Movements in Sleep

To obtain the PLMI, the American Academy of Sleep Medicine has standardized methods for recording and scoring PLMs in sleep (AASM, 2007):

“A. The following rules define a significant leg movement (LM) event:
   1) The minimum duration of a LM event is 0.5 seconds.
   2) The maximum duration of a LM event is 10 seconds
   3) The minimum amplitude of a LM event is an 8µV-increase in EMG voltage above resting EMG.
   4) The timing of the onset of a LM event is defined as the point at which there is an 8µV-increase in EMG voltage above resting EMG.
   5) The timing of the ending of a LM event is defined as the start of a period lasting at least 0.5 seconds during which the EMG does not exceed 2µV above resting EMG.

B. The following rules define a PLM series:
   1) The minimum number of consecutive LM events needed to define a PLM series is 4 LMs.
   2) The minimum period length between LMs (defined as the time between onsets of consecutive LMs) to include them as part of a PLM series is 5 seconds.
   3) The maximum period length between LMs (defined as the time between onsets of consecutive LMs) to include them as part of a PLM series is 90 sec.
   4) Leg movements on 2 different legs separated by less than 5 seconds between movement onsets are counted as a single leg movement.”

Notes:
1. A LM should not be scored if it occurs during a period from 0.5 seconds preceding an apnea or hypopnea to 0.5 seconds following an apnea or hypopnea.

2. An arousal and a PLM should be considered associated with each other when there is < 0.5 seconds between the end of one event and the onset of the other event regardless of which is first.

3. Surface electrodes should be placed longitudinally and symmetrically around the middle of the muscle so that they are 2 to 3 cm apart or one third of the length of the anterior tibialis muscle, whichever is shorter. Both legs should be monitored for the presence of the leg movements. Separate channels for each leg are strongly preferred. Combining electrodes from the two legs to give one recorded channel may suffice for some clinical settings, though it should be recognized that this strategy may reduce the number of detected LMs. Movements of the upper limbs may be sampled if clinically indicated.

4. The rules in “A” above define a significant leg movement event by absolute increase in μV above resting baseline for the anterior tibialis EMG. This requires a stable resting EMG for the relaxed anterior tibialis whose absolute signal should be no greater than +10μV between negative and positive deflection (±5 μV) or +5 μV for rectified signals.

5. Use of 60 Hz (notch filters) should be avoided. Impedances need to be less than 10,000Ω. Less than 5,000Ω is preferred but may be difficult to obtain. Sensitivity limits of -100 and 100μV (upper/lower) are preferred.”

(AASM Manual for Scoring Sleep, 2007, p. 41)

Following the rules above, breathing events must be scored first to rule out LMs associated with apneas or hypopneas. An apnea is defined as a 90% or greater decrease in airflow for at least 10 seconds and a hypopnea is defined as a 50% or greater decrease in airflow for at least 10 seconds associated with a drop in blood oxygen saturation of 3% or more (American Academy of Sleep Medicine, 2007).

Currently, in the Sleep Laboratory at Kingston General Hospital, scoring of limb movements according to the above rules is done through visual inspection (personal communication, H. Driver, November, 2010). This is also the case at one of the major RLS research laboratories in North America, the Centre D’Etude du Sommeil in Montreal (personal communication, S. Frenette, May 2011). The Sandman recording and analysis software in use at Kingston General Hospital Sleep Laboratory does perform automated scoring of events but the events are always confirmed visually by PSG technologists, which is in accordance with the AASM Standards for Accreditation of Sleep Disorders Centres (2011).
2.3.4 Reliability of scoring PSG recordings

Research in the area of inter-rater and intra-rater reliability for scoring of PSG recordings has shown mixed results (Collop, 2002; Whitney et al., 1998). Collop (2002) examined inter-rater reliability among 11 PSG technologists working in nine different sleep laboratories throughout North America. All centres utilized the same collection software, but no data were obtained on scoring rules in use at each centre. Technologists’ years of experience ranged from three to eleven. Analysis yielded a kappa statistic of 0.31 for total apneas and hypopneas scored for all studies and scorers. No significance level or confidence intervals were given. This result indicates only fair agreement between scorers in this study, but the low reliability could be due to multiple factors including varied levels of experience and non-standardized scoring rules and definitions. Among the recommendations of this study were to ensure regular quality management testing of technologists’ scoring within a centre and standardization of PSG scoring rules (Collop, 2002).

In contrast, Whitney et al (1998) found much higher levels of inter-rater reliability with more standardized scoring. They examined reliability during the first stages of the Sleep Heart Health Study (Quan, et al., 1997), during which participants underwent in-home, unattended overnight sleep studies for the screening of Obstructive Sleep Apnea (OSA). Three PSG technologists, all with the same training, and experience of having scored at least 80 studies with the standardized criteria (per Sleep Heart Health Study Reading Centre manual of operations, 1996) scored 20 records visually for respiratory events (with no EEG data). ICC value for inter-rater reliability in scoring respiratory events was 0.97 (using a 3% decreased blood oxygen saturation rule); no confidence interval or significance level were given (Whitney et al., 1998). Intra-rater reliability was examined by t-test. One scorer identified, on average, significantly more respiratory events on their second analysis of the same 20 records; mean difference -0.85 ±
1.26, p < 0.001, whereas the other two did not (Whitney et al., 1998). Further reliability analysis, such as ICC values, with confidence intervals, would provide a clearer picture of the intra-rater reliability in this group.

The AASM has produced voluntary Standards for Accreditation of Sleep Disorders Centres (2011) in which they stipulate that inter-rater comparisons must be made between each scorer in a facility and a designated Sleep Specialist on a minimum of 12 PSG records per year. Records must be kept on inter-rater reliability for each scorer, though a benchmark value is not suggested (AASM, 2011).

No studies were identified that examined inter-rater or intra-rater reliability for scoring PLMI by PSG or portable monitor, but it is reasonable to postulate that reliability in this task would also be subject to issues of experience and standardization. This is an area that merits further exploration.

2.3.5 Periodic Limb Movement Disorder

Mention should also be made of a condition known as Periodic Limb Movement Disorder (PLMD), which also presents with the same type of stereotypical leg movements during sleep as RLS (AASM, 2005). However, there are no subjective complaints of lower limb discomfort or urges to move as are associated with RLS. Individuals with PLMD would have none of the four essential criteria for the diagnosis of RLS (AASM, 2005). According to the International Classification of Sleep Disorders (AASM, 2005), for a diagnosis of PLMD, an individual must have a PLMI of at least 25 during an overnight sleep study.

2.3.6 RLS-diagnostic index (RLS-DI).

Diagnosis of RLS remains primarily a clinical judgment made by experienced medical specialists, usually based on subjective reports of patients (Trenkwalder, Hogl & Winkelman,
The specificity of the IRLSSG criteria is not perfect and cannot always rule out leg symptoms due to other conditions (Hening, Allen, Washburn, Lesage & Earley, 2009). The very subjective nature of the diagnostic criteria may leave primary care practitioners feeling unclear about the condition. This may explain in part why RLS is under diagnosed in routine practice (Allen et al., 2005).

The difficulties in efficiently coming to a clear diagnosis in RLS cases has led to the development of a standardized diagnostic tool, the RLS-DI (Appendix 7.5), which can be utilized by non-experts equally as well as experts (Benes & Kohnen, 2009). The RLS-DI is a questionnaire that gives differential weighting to the presence or absence of the major RLS criteria and the supportive factors mentioned above. Benes & Kohnen (2009) examined the validity of this tool as used by trained non-expert interviewers in comparison to the “gold standard” of expert clinical interview. Scores on the RLS-DI can range from -22 (no RLS) to 20 (definite RLS). A cut-off score of ≥11 was determined for the diagnosis of RLS (Benes & Kohnen, 2009). The inclusion of the supportive features, especially the presence of PLMs and history of response to dopamine agonist significantly increased the specificity of the tool for diagnosing RLS. The distribution of RLS-DI total scores demonstrated the ability of the tool to identify individuals with RLS from those with other conditions with a sensitivity of 93% and specificity of 98.9% and a total accuracy of 96.1% (Benes & Kohnen, 2009). Analysis of the essential criteria sub score alone (without the supportive criteria) only yielded a specificity of 81% for diagnosing RLS (Benes & Kohnen, 2009). Clearly, PLM measurement should be routine in suspected RLS to ensure a correct diagnosis.

2.3.7 Accessibility of sleep studies.

Currently, the standard method to measure PLMI is via polysomnography (PSG), which requires an overnight stay at a sleep laboratory (Allen et al., 2003). The cost of a one-night sleep
study in Ontario is currently $384 (personal communication, H. Driver, June 2011). Wait times for a sleep study in Ontario vary by centre, but Rotenberg et al (2010) found an average time of 4.9 months from referral. Requiring PSG studies for clinical diagnosis of RLS is expensive, inconvenient and may be impractical in many situations.

2.3.8 Suggested Immobilization Test

In both clinical situations and research studies, having to obtain a PSG as an objective measure impedes the diagnosis of RLS and detection of change with treatment. Clearly there is a need for more practical, efficacious methods to evaluate PLMs.

A research group based at the Centre d’Etude Du Sommeil in Montreal, Canada designed the Suggested Immobilization Test (SIT) as an alternative procedure, and first published a report on its use as an objective measure in the study of RLS in 1988 (Brodeur et al., 1988, cited in Montplaisir et al., 1998). The design of this procedure was based on the fact that symptoms are known to be worse at rest and in the evenings (Montplaisir et al., 1998). This procedure requires the individuals with suspected RLS to maintain immobility for an hour in the late evening (after 9pm) while experiencing the possible RLS symptoms.

As described by Montplaisir et al (1998), the SIT procedure requires individuals to sit in bed awake, reclined to 45° with the legs outstretched, and to try to avoid moving for the duration of the test (one hour). They are prompted every 5 minutes to record their level of leg discomfort using a Visual Analog Scale (VAS) of 0 to 100, 0 being no discomfort and 100 constituting the worst discomfort. In the original version of the SIT, the individuals were monitored via video for alertness and generalized movement. Surface EMG of bilateral tibialis anterior muscles was recorded to detect PLMs and some EEG channels were monitored to detect whether the person was awake or asleep. The SIT was typically performed in the later evening (~ 9pm) to coincide
with the time of day that waking RLS symptoms are generally found to be worst (Montplaisir et al., 1998).

In the original study (Montplaisir, 1998) PLMs were recorded from 16 participants with RLS and age/sex-matched controls during the SIT and PSG on two consecutive nights. During the SIT, PLMs were three times more numerous in the participants with RLS than in controls (76.1 ± 9.6 versus 26.9 ± 7.8, p < 0.001); the leg movements were predominately bilateral, and the number of limb movements was much higher in the second half of the test (Montplaisir, 1998). Cut off value for diagnosis of RLS with the SIT was determined to be an Index (total number of limb movements during the one hour test) of 40 (Montplaisir, 1998). For this small group of participants with severe RLS, the sensitivity and specificity of the SIT Index were both 81% (Montplaisir, 1998).

However, a follow-up study with 100 participants with RLS of varying severity, and 50 controls by Michaud, Paquet, Lavigne, Desautels & Montplaisir (2002b) found that a SIT PLM ≥ 11 best discriminated participants with RLS from controls; specificity = 84%, sensitivity = 62%. They concluded that in populations with a range of RLS severity, this cutoff value was more appropriate (Michaud et al., 2002b). Additionally in this study, measurement of leg discomfort using a visual analog scale (VAS) was done during the SIT and a mean score of leg discomfort during the test was obtained. This leg discomfort score (cut-off > 11) was also shown to correctly classify RLS in over 80% of RLS cases with a specificity of 84% and sensitivity of 82% (Michaud et al., 2002b).

Michaud, Poirier, Lavigne & Montplaisir (2001) examined scoring of the PLMs during SIT. PLMs during the SIT were also noted to have the same periodicity and interval characteristics as PLMs during sleep. Thus criteria for scoring SIT PLMs are exactly the same as
for scoring PLMs during sleep, without the exceptions for breathing and arousal associated limb movements, as the individual is not asleep (Michaud et al., 2001).

Concerns about test-retest reliability of the SIT have been explored by Haba-Rubio & Sforza (2006). Their study repeated the SIT in 20 individuals with primary RLS on two consecutive evenings followed by overnight PSG studies. It was noted that the evolution of motor activity during the SIT was very consistent during both tests, with a significant rise as the test progressed. Additionally, although the SIT PLM was not significantly different between the two tests, there were large intra-individual differences; SIT PLM rose from 40.3± 45.4 in the first test to 61.6± 67.5 in the second (p=0.17) (Haba-Rubio & Sforza, 2006). However the authors did not provide a statistical analysis of the absolute test-retest reliability. This large variation in PLMs test to test is not specific to the SIT however, as the same intra-individual variability is also evident in PSG studies (Allen, 2007a).

2.3.9 Assessment with Portable Devices

Movement measurement or actigraphy has been widely used to monitor sleep outside of the laboratory (Van de Water, Holmes, & Hurley, 2011). One actigraph has been developed specifically for PLM measurement, the PAM-RL®. Developed by Dr. R. Allen, a lead researcher in the field of RLS, in conjunction with IM Systems, it is marketed by Resprionics (Allen, 2007a). This device is worn around the ankle and measures movement of the lower limb through a tri-axial accelerometer. A body position sensor detects whether the person is upright so that movements related to standing and walking can be excluded from the PLM scoring. The device has accompanying software, which automatically “scores” the movements and calculates a PLMI of limb movements per hour of sleep (http://pamrl.respironics.com/features.asp).

Sforza, Johannes & Claudio (2005) examined the degree of agreement between numbers of limb movements detected by the PAM-RL® and by PSG in population of individuals referred
to a sleep laboratory for sleep related disorders. They determined a significant correlation between PSG PLMI and actigraphy PLMI using the PAM-RL® (r=0.87, P< 0.0001) (Sforza, Johannes & Claudio, 2005). In a subgroup of five participants with RLS there was close agreement between consecutive night scores using the PAM-RL® (r=0.90, P ≤0.05) (Sforza, Johannes & Claudio, 2005). Given that PSG scoring was done by visual inspection of the records and the PAM-RL® scoring is automated, Allen (2007a) concluded that these results also support the validity of the automatic computerized scoring. Sforza, Johannes & Claudio (2005) did note that the device was not as reliable in participants with sleep related breathing disorders and insomnia. Sixty percent of participants diagnosed with sleep related breathing disorders had a PLMI greater than the cut-off for RLS (Sforza, Johannes & Claudio, 2005). These individuals would have a high percentage of non-PLM movement that would artificially boost the PLMI value.

A major benefit of using a limb activity monitor is the ability to wear it over several nights consecutively and determine a peak PLMI value. This approach may minimize error due to the inherent variability in the occurrence of PLMs day to day (Allen, 2007a). However, actigraphy has significant limitations for comparison with PSG. No breathing events or blood oxygen saturation levels are captured (Gschliesser et al., 2009). Thus a limb activity monitor is an indirect measure of PLMs as defined and scored by AASM criteria, so lacks criterion validity as a substitute measure for PSG (Portney & Watkins, 2009).

Another approach is to use a portable sleep monitor of which there are several types available (Ahmed, Patel, & Rosen, 2007). The Medibyte®, a portable sleep monitor developed by a Canadian company (Braebon of Kanata, Ontario), has been validated against PSG for use as a home sleep apnea screening device (Driver et al., 2011). The Medibyte® also has auxiliary channels that can be used to collect EMG data for bruxism (teeth grinding) or limb movements.
A portable sleep monitor that records respiratory events and EMG would allow more precise and accurate PLM measurements than a limb activity monitor, as LMs associated with apneas and with walking could be excluded from a PLM count. This method would be preferable over limb activity monitoring in isolation as it provides data that much more closely aligns with the AASM scoring criteria for PLMs (Gschliesser et al., 2009).

### 2.3.10 The Braebon Medibyte as a potential PLM recording device

The sampling frequency of the EMG recording sensor of the Medibyte® is of concern regarding the validity of this device for detecting PLMs. The World Association of Sleep Medicine (WASM) (Zucconi et al., 2006) recommends an EMG sampling frequency of 200Hz for clinical studies and 400 Hz in research studies for detection of PLMs. The Medibyte® samples the EMG signal at 250Hz (http://www.braebon.com/products/medibyte/), which is low by these standards and much lower than the 1000Hz standard recommended for surface EMG studies by the International Society of Electrophysiology and Kinesiology (ISEK) (DeLuca, 2003). This low sampling rate could cause inaccurate recording of limb movements (DeLuca, 2003).

Secondly, EMG recordings of the right and left legs are combined into one recorded channel prior to analysis. This is discouraged in the WASM Standards (Zucconi et al., 2006), which state that bilateral recordings are required for research in particular. The impact of these deficiencies is a potentially inaccurate reproduction of the sample signal (De Luca, 2001) and thus an altered detection rate of PLMs.

ISEK Standards for Reporting EMG Data state that “The minimal acceptable sampling rate is at least twice the highest frequency cut-off of the band pass filter used .... as specified by Nyquist Theorem. Sampling rates below twice the highest frequency cut-off are incorrect” (Merletti, 1999). Surface EMG signals are reported to contain frequencies up to 1000Hz (Winter,
or as DeLuca (2002) stated, “The usable energy of the signal is limited to the 0 to 500 Hz frequency range,” (p. 2). According to the Nyquist Theorem then, surface EMG should be sampled at no lower than 1000Hz or 2000Hz. This requirement is to prevent “aliasing”, which is the introduction of false frequencies into the signal that would potentially invalidate the detection of muscle activity by the EMG channel (De Luca, 2001).

2.3.10.1 Nyquist sampling theorem

To understand the concept of aliasing and how it could occur, consider a signal composed of a single sine wave at a frequency of 1 Hz (Figure 2-1a). If samples of this are taken at 2 Hz (as dictated by the Nyquist theorem), every peak and trough of the sine wave is captured (Figure 2-1b). Sampling at a higher frequency (3 Hz) offers more than enough information to re-create any variation in the signal (Figure 2-1c). However, once the sampling frequency drops below twice the highest frequency in the signal, there is not enough information to properly recreate the signal. Some of the peaks and troughs of the wave are lost (Figure 2-1d). This leads to the false representation of the original signal or “aliasing” (Figure 2-1e) (Olshausen, 2000).
Figure 2-1c One Hz sine wave sampled at 3 Hz

Figure 2-1d One Hz sine wave sampled at 1.5 Hz

Figure 2-1e One Hz sine wave re-created when sampled at 1.5 Hz

Figure 2-1 the 1Hz sine wave recreated when sampled at 1.5 Hz now appears to be a 2 Hz sine wave (Figures 2-1a to 2-1e adapted from Aliasing, Bruno A. Olshausen, 2000, http://redwood.berkeley.edu/bruno/npb261/aliasing.pdf retrieved May 29/12 1:42pm)

An anti-aliasing filter is frequently used to overcome the problem of potential aliasing in a recorded signal (DeLuca, 2001). This type of filter essentially attenuates all signals above a set frequency and should be set at a frequency that is one half the sampling frequency, thereby reducing potential aliasing occurring in the recorded signal (DeLuca, 2001).

2.4 Significance Of These Studies

The quantification of change in RLS status is challenging, both subjectively and especially objectively. To justify interventions for RLS that we may wish to trial, we must be confident that our measurement methods and tools are valid and reliable for the purpose, and are
practical to be used easily and widely in both clinical and research applications. The current objective standard, overnight PSG, has many concerns in this regard.

These studies propose to answer the following questions:

1. Is the Medibyte® portable sleep monitor with surface EMG channels able to accurately record bilateral tibialis anterior contractions in comparison with the gold standard, a recognized surface EMG amplifier and software collection system? (Study 1)

2. Can the auxiliary EMG channel of the Medibyte® be utilized to accurately record PLMs and what is the degree of agreement between Medibyte PLMI and PSG PLMI? (Study 2)

3. What is the intra-rater reliability for scoring Medibyte® records for PLMI? (Study 2)

4. What is the inter-rater reliability for scoring Medibyte® records for PLMI? (Study 2)
Chapter 3

Validity of the Medibyte for recording surface EMG

3.1 Study 1 Research Question

To determine the validity of the Medibyte® as a tool for the purpose of measuring PLMs, concerns regarding the sampling frequency were addressed through comparison of the Medibyte® with standard surface EMG collection. The research question was:

Despite a lower than Nyquist sampling rate, does the Medibyte® accurately record bilateral tibialis anterior muscle activity in comparison to standard surface EMG as recorded by the Bortec AMT-8® EMG Amplifier?

3.2 Introduction & Rationale

The presence of PLMs is a key confirmatory measure of the diagnosis and severity of RLS. These are involuntary rhythmic movements of the lower legs that occur during sleep (Allen et al., 2003). The standard method to measure PLMs is via polysomnography (PSG), which requires an overnight stay at a sleep laboratory (Allen et al., 2003). However, requiring PSG studies for clinical diagnosis involves long wait times (Rotenberg et al., 2010) is impractical, inconvenient, and in RLS research studies, is likely to have a negative impact on recruitment.

A potential solution to this problem may be the use of a portable home sleep monitor. The Medibyte® is a novel unit developed by a Canadian company (Braebon of Kanata, Ontario), which has been validated against PSG for use as a home sleep apnea screening device (Driver et al., 2011). The Medibyte® also has auxiliary channels that can be used to collect EMG data for bruxism (teeth grinding) or limb movements (http://www.braebon.com/products/medibyte/).

However, the Medibyte® has potential limitations for EMG recording of PLMs. The
World Association of Sleep Medicine (WASM) (Zucconi et al., 2006) recommends an EMG sampling frequency of 200Hz for clinical studies and 400 Hz in research studies for detection of PLMs. The EMG recording sensor of the Medibyte® samples at 250Hz ((http://www.braebon.com/products/medibyte/). Secondly, EMG recordings of the right and left legs are combined into one recorded channel prior to analysis. This is discouraged in the WASM Standards (Zucconi et al., 2006), which state that bilateral recordings are required for research in particular.

The International Society of Electrophysiology and Kinesiology (ISEK) Standards for Reporting EMG Data (Merletti, 1999) are more rigorous, stating that “The minimal acceptable sampling rate is at least twice the highest frequency cut-off of the band pass filter used .... as specified by Nyquist Theorem. Sampling rates below twice the highest frequency cut-off are incorrect” (Merletti, 1999). Surface EMG signals are known to contain frequencies up to 1000 Hz (Winter 2005); however, according to DeLuca (2002) “The usable energy of the signal is limited to the 0 to 500 Hz frequency range” (p. 2). Thus, by the rules of the Nyquist Theorem, surface EMG should be sampled at no lower than 1000Hz. This requirement is to prevent aliasing, which is the introduction of false frequencies into the signal that would potentially invalidate the recording as a true representation of the muscle activity (De Luca, 2001).

### 3.2.1 Study Objective

The objective of this study is to determine if the Medibyte® portable sleep monitor with surface EMG channels is able to accurately record bilateral tibialis anterior contractions in comparison with the gold standard, a recognized surface EMG amplifier and software collection system.
3.3 Methods

3.3.1 Study design

To clarify whether aliasing does occur in the Medibyte® EMG signal, EMG data of bilateral tibialis anterior activity was collected simultaneously by both the Medibyte® EMG channel and the Bortec EMG Amplifier. The recordings were compared for counts of muscle activity.

3.3.2 Instrumentation

3.3.2.1 Medibyte® Portable Monitor

The Medibyte® device is marketed as a “home sleep lab that fits in the palm of your hand.” (Figure 3-1) (http://www.braebon.com/products/medibyte/specs.php, retrieved June 8, 2011, 11:17am). It was developed by Braebon of Kanata Ontario for the home screening of OSA. It weighs approximately three ounces, has channels for measurement of respiratory effort (chest and abdomen), blood oximetry, nasal airflow, heart rate, snore audio, body position (3 axis accelerometer), event marker, and auxiliary channels for EMG (Braebon Medical Corporation, 2011). Two Respiratory Inductive Plethysmography (RIP) belts measure respiratory effort. A SpO2 cable with a silicone finger pouch tracks blood oximetry and pulse. Figure 3-2 shows how the unit is worn for an overnight sleep study. Snore audio, nasal airflow and respiratory effort were not necessary for this research. The SpO2 cable was used, as the device would not record without it attached. The Event button on the front of the Medibyte® unit will mark a line on the recording indicating the time the button was pressed (Braebon Medical Corporation, 2011).
**Figure 3-1** Medibyte® dimensions: 2.5 x 2.25 x 0.75 inches (66 x 60 x 19mm)

(Reproduced from the Braebon website, with permission; http://www.braebon.com/products/medibyte/specs.php)

The Medibyte processing unit is worn on the chest respiratory effort belt.

**Figure 3-2** Medibyte® portable monitor set up for OSA screening (Medibyte® Patient Guide 2010 – reproduced with permission)

The unit uses a 24bit Analog to Digital card for conversion of the signals from analog to digital format for processing (http://www.braebon.com/products/medibyte/specs.php). There is
no mention of whether the EMG signal (250Hz sampling frequency) is rectified. There is no low pass filter (allows all lower frequencies to be captured) in the monitor but there is a 125 Hz anti-aliasing filter (personal communication with D. Bradley, Medibyte® developer, June, 2012). The monitor has a high pass filter (allows all higher frequencies to be captured) at 0.73 Hz and a notch filter at 60 Hz (to eliminate electrical “noise” from nearby equipment). The software incorporates a high pass filter of 10 Hz (personal communication with D. Bradley, Medibyte® developer, June, 2012). Therefore, the monitor will only record frequencies between 10 Hz and 125 Hz, (even though it is sampling up to 250 Hz), with the exception of frequencies at 60 Hz.

3.3.2.2 Bortec AMT-8® EMG System

The Bortec EMG AMT-8® Amplifier has up to eight channels for detecting EMG, with an input impedance of 10 GOhms and a Common Mode Rejection Ratio of 115 dB at 60 Hz, bandwidth 10-1000Hz (Bortec Biomedical Limited, 2011) (see figure 3-3).

![Figure 3-3 Bortec AMT-8® Amplifier (photo credit M.J. O’Donovan)](image)
Each channel was pre-amplified with inline preamplifiers. These pre-amplified leads are described on the Bortec Biomedical© website as follows:

“APE-500 is a high impedance differential amplifier with a standard gain of 500. The main purpose of the pre-amplifier is to amplify the EMG signal and suppress common mode noise. The pre-amplifiers amplify and condition the EMG signal by converting the signal from high impedance to low impedance, effectively eliminating cable noise in the transmission of the signal” (Figure 3-4) (Bortec Biomedical Limited, 2011).

Figure 3-4 Bortec® APE500R pre- amplifier and leads (photo credit M.J. O’Donovan)
The raw data was acquired by Delsys\textsuperscript{TM} EMG Acquisition software with a 16-bit National Instruments\textsuperscript{TM} analog to digital (AD) converter (NDAQPCI-MIO-16XE-10). Table 3-1 provides a summary of the EMG collection specifications of the two systems being compared.

<table>
<thead>
<tr>
<th></th>
<th>BORTEC AMT-8 EMG AMPLIFIER\textsuperscript{®} WITH DELSYS EMG WORKS\textsuperscript{®} ACQUISITION SOFTWARE</th>
<th>MEDIBYTE\textsuperscript{®} EMG PROCESSOR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sampling frequency</td>
<td>2000Hz</td>
<td>250Hz</td>
</tr>
<tr>
<td>Impedance</td>
<td>10GOhms</td>
<td>Not specified</td>
</tr>
<tr>
<td>Rectification</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>Filtering</td>
<td>Band pass filter – 10 -500 Hz</td>
<td>High pass – 10 Hz</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Anti-aliasing – 125 Hz</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Notch filter – 60 Hz</td>
</tr>
<tr>
<td>Analog-Digital</td>
<td>16 bit</td>
<td>24 bit</td>
</tr>
<tr>
<td>Conversion Ratio</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Common Mode Rejection</td>
<td>115Db</td>
<td>Not specified</td>
</tr>
</tbody>
</table>

\textbf{Table 3-1} Summary of EMG data acquisition specifications with each system

\textbf{3.3.3 Participants}

Participants consisted of a sample of convenience of five healthy adults ranging in age from 20-50 years with no neurological or musculoskeletal dysfunction of the lower limbs. All participants were female.

\textbf{3.3.4 Procedures}

This project received Ethics clearance through the General Ethics Research Board application short form for Course-Based Student Research (Appendix 7.7). All participants signed an informed consent form (Appendix 7.6). EMG signal collection was with 2 pairs of
Kendall® EKG type single use AG/AgCl adhesive electrodes bilaterally, located over each tibialis anterior muscle, 2 cm apart. The electrodes were placed longitudinally on the muscles, in the upper third of the muscle. A reference electrode was placed on the lateral malleolus of the right ankle (see Figure 3-5). Skin preparation consisted of vigorous rubbing of the skin with alcohol swabs.

![Reference electrode for surface EMG collection](image)

**Figure 3-5** Equipment set up for surface EMG collection for Study 1. Recording of bilateral tibialis anterior activity by Medibyte® and Bortec AMT-8®. (photo credit – MJ O’Donovan)
Splitter connections were constructed (see Figure 3-6) to allow EMG signals to be transmitted simultaneously to both the Medible® and the Bortec® EMG amplifier.

![Splitter connections](image)

**Figure 3-6** Splitter connections allowing simultaneous collection of EMG by Medible® and Bortec AMT-8® with one set of electrodes. (photo credit - MJ O'Donovan)

Recording began with participants at rest. They then performed a series of bilateral ankle dorsiflexion and great toe extension movements that simulated PLMs. A total of 20 each of full range simultaneous bilateral ankle dorsiflexion, half-range dorsiflexion and full range great toe extension movements were completed. Each participant was given the opportunity to practice each movement several times prior to recording to facilitate a standardized level of contraction for each repetition. The timing of these movements simulated the periodic limb movements that occur in RLS. Each movement lasted between 0.5 and 10 seconds. The period length (time from onset of one movement to onset of the next movement) for two consecutive movements was between 1 second and 90 seconds. Participants pressed the event button on the Medible® each time they performed a movement to mark the Medible® tracing for analysis purposes. This event marker would clearly indicate when contractions should be noted on the tracing.

With the Bortec recording of the muscle activity, the surface EMG data were amplified (1000x), band pass filtered from 10 Hz to 500 Hz, and sampled at 1kHz. There was no post-processing of the raw data.
3.3.5 Data Analysis

Both Medibyte® and Bortec® recordings were inspected visually and manual counts made of every burst of increased EMG activity. On the Medibyte® tracing, note was made of all “events” recorded by the portable monitor event button. These were checked to determine their relationship to the EMG activity recorded. Figures 3-7 and 3-8 below are sample Bortec® and Medibyte® tracings of tibialis anterior muscle activity.

![Figure 3-7 Bortec® recording – EMG only](image1)

![Figure 3-8 Medibyte® recording. Leg muscle activity is recorded on the top tracing. Note other information recorded by the device](image2)
3.4 Results

Participant demographic information is presented in Table 3-2. The mean age was 24.6 years ± 6.6; mean height and weight were 1.68m ± .08 and 59.8Kg ± 6.84.

<table>
<thead>
<tr>
<th>PARTICIPANT AGE</th>
<th>PARTICIPANT HEIGHT (M)</th>
<th>PARTICIPANT WEIGHT (KG)</th>
<th>PARTICIPANT BMI</th>
</tr>
</thead>
<tbody>
<tr>
<td>36</td>
<td>1.64</td>
<td>63.5</td>
<td>23.6</td>
</tr>
<tr>
<td>23</td>
<td>1.70</td>
<td>62.7</td>
<td>21.7</td>
</tr>
<tr>
<td>20</td>
<td>1.68</td>
<td>51.0</td>
<td>18.1</td>
</tr>
<tr>
<td>20</td>
<td>1.60</td>
<td>54.5</td>
<td>21.3</td>
</tr>
<tr>
<td>24</td>
<td>1.80</td>
<td>67.5</td>
<td>20.8</td>
</tr>
</tbody>
</table>

Table 3-2 Participant demographics. M= metres; KG = kilograms; BMI = Body Mass Index

Participant contraction counts obtained from each device, the Braebon Medibyte® and the Bortec EMG Amplifier, are shown in Table 3. It is immediately evident that both systems detected equal numbers of contractions. All bursts of EMG activity noted on the Medibyte® recording corresponded to an “event” mark. There was complete agreement between the two systems for all 5 participants, and both of these systems agreed completely with the actual number of movements as indicated by the event marker.
Table 3-3 Comparison of contraction counts

<table>
<thead>
<tr>
<th>PARTICIPANT</th>
<th>BORTEC CONTRACTION COUNT</th>
<th>MEDIBYTE® CONTRACTION COUNT</th>
</tr>
</thead>
<tbody>
<tr>
<td>01</td>
<td>40</td>
<td>40</td>
</tr>
<tr>
<td>02</td>
<td>61</td>
<td>61</td>
</tr>
<tr>
<td>03</td>
<td>60</td>
<td>60</td>
</tr>
<tr>
<td>04</td>
<td>59</td>
<td>59</td>
</tr>
<tr>
<td>05</td>
<td>60</td>
<td>60</td>
</tr>
</tbody>
</table>

3.5 Discussion

3.5.1 Key Findings

The purpose of this study was to determine if, despite a lower than Nyquist sampling rate, the Medibyte® EMG channel was able to accurately record bilateral tibialis anterior muscle activity (simulated PLMs) in comparison to standard surface EMG as recorded by the Bortec AMT-8® EMG Amplifier. It was hypothesized that due to a potential aliasing effect, there could be a mismatch between the muscle burst frequency counts between devices. The data indicate that there is perfect agreement between the counts recorded by each device. Thus despite concerns regarding sampling frequency, it is evident that the Medibyte® is able to accurately record the presence of even small PLM type (toe extension) contractions.

3.5.2 Surface EMG collection

The primary EMG collection concern was related to the low sampling rate of the EMG signal (250Hz). This rate is essentially invalid for measuring EMG, which can have frequencies up to 1000 Hz (DeLuca, 2001). According to the Nyquist Theorem, the sampling frequency of a
signal must be at least twice the rate of the highest frequency in the signal of interest (DeLuca, 2001). If sampled lower than this, the recorded signal may have false frequencies in it that are not actually present in the signal sampled (DeLuca, 2001). This is known as aliasing. The risk of aliasing occurring in the recorded EMG signal potentially invalidates the use of Medibyte® for EMG detection and therefore PLM counts. The results of this study suggest that the Medibyte® device does not suffer from any aliasing concerns that would impact detecting and counting PLMs.

Two factors are proposed to explain the ability of the Medibyte® EMG channel to accurately record PLM type muscle activity. First, in follow-up to this study, the investigator (M.J.O’D.) contacted a Braebon representative, the company that produces the Medibyte®, who revealed that the device includes a 125Hz anti-aliasing filter. This information is not included in any of the company literature promoting the device and was not available at the time of initial testing. The inclusion of the 125Hz anti-aliasing filter in this device does minimize the possibility of aliasing. However, this filter could also potentially affect the accuracy of the recorded signal as surface EMG signals are reported to contain frequencies up to 1000Hz (Winter, 2005) or as DeLuca (2002) states, “The usable energy of the signal is limited to the 0 to 500 Hz frequency range,” (p. 2). Thus, the anti-aliasing filter of the Medibyte® would eliminate most of the frequencies in the higher range of the EMG signal. However, the largest proportion of the signal in surface EMG is reported to be below 200 Hz (Winter, 2005), or in the 50-150 Hz range (De Luca, 2002) so most of the signal is preserved and would still be represented in surface EMG recordings collected by the Medibyte®. Thus it is possible that under sampling by the Medibyte® EMG channel may not distort the signal information enough to limit its accuracy for the purposes of straightforward detection of presence or absence of muscle activity.
Conversely, it has been shown that in the unprocessed EMG signal under sampling likely impacts characteristics such as amplitude and duration. Ives and Wigglesworth (2003) explored the effect of sampling rate on visually determined onset detection and burst duration in a signal recorded at 6000Hz and then resampled without any anti-aliasing filters at 3000, 1000, 500 and 250 Hz. They found that in a full wave rectified signal, time of visual onset detection was significantly different between 250Hz (96.8 ± 20.8 milliseconds) and 1000Hz (100.2 ± 26.1 milliseconds) (p < 0.003). Visually determined burst duration was also significantly different between 250Hz (2177.4 ± 162.8 milliseconds) and 1000Hz (2159.2 ± 157.9 milliseconds) (p < 0.05). There was no significant difference in burst duration between sampling rates if the signal was first smoothed (Ives and Wigglesworth, 2003). They suggested minor “under-sampling at 500Hz does not automatically invalidate timing amplitude data if the sEMG (surface EMG) signal has been appropriately smoothed” (Ives & Wigglesworth, 2003, p. 548-549) and concluded with the suggestion that it would be useful to re-examine this type of data with the use of an anti-aliasing filter to determine if these results would still hold true.

Considering the Medibyte® EMG channel in light of this information, it would appear that timing variables of the EMG signal might potentially be distorted. This could impact PLM measurements collected using this device. Further testing was needed to clarify this issue.

### 3.5.3 Periodic Limb Movement Measurement

To reliably and accurately detect periodic limb movements that are associated with RLS, the American Academy of Sleep Medicine has set the following standards as of 2007. To be scored as a PLM, the EMG burst on the recording must meet these criteria:

- a greater than 8µV increase from baseline EMG levels;
- a duration of at least 0.5 seconds and not longer than 10 seconds;
- interval between contractions must be at least 0.5 seconds;
• period from onset of one contraction to the next at least 5 seconds but not longer than 90 seconds;
• these movements must occur in groups of 4 (all meeting the above criteria);
• movements are not scored if they occur in within the period 0.5 seconds prior to or 0.5 seconds after breathing events (apnea/hypopneas);
• are often presented as PLMS (sleep) vs. PLMW (wake).

Thus the accuracy of the Medibyte® EMG channel in recording amplitude and duration variables of the EMG activity impacts its validity as a tool to measure PLMs. The ability to accurately score limb movements according to the above criteria is addressed in Study 2.

3.5.4 Study Limitations

This study represents a preliminary examination of one element of the concerns regarding the use of the Medibyte® device for the home measurement of PLMs. Questions still remain regarding criterion validity and reliability of this device for the assessment of PLMI. The sample size was very small and the numbers of contractions (~60/participant) also somewhat low compared to numbers of limb movements potentially seen in an overnight sleep study. PLMI values have been documented as high as greater than 60/hour overnight (Sforza, Johannes, & Claudio, 2005). Despite the perfect agreement in values between the two methods of EMG signal sampling in this study, the Medibyte® requires further testing in overnight sleep studies.

3.6 Conclusion

The results of this study confirm that the Medibyte® EMG channel for limb movement is able to detect all incidences of tibialis anterior contraction as detected by standard surface EMG (Bortec AMT-8 EMG Amplifier). The Medibyte® home sleep study unit is therefore potentially able to accurately detect muscle contractions of the tibialis anterior for use in the home.
measurement of PLMs. Comparison of Medibyte® derived PLMI to the current standard of PLMI obtained through overnight PSG study should also be performed to determine the level of agreement between these measures.

Pending the work of this further study, the Medibyte® portable sleep monitor may prove to be a useful tool to aid in the diagnosis and study of RLS. It is postulated that this device would provide a convenient accessible alternative to PSG for obtaining objective outcome measures of RLS severity.
Chapter 4

Reliability and Validity of the Medibyte for recording limb movements in comparison with PSG

4.1 Study 2 Research Questions

The results of Study 1 established the ability of the portable monitor to accurately record tibialis anterior muscle activity. To establish concurrent validity of the monitor for the measurement of PLMs and obtaining a PLM Index (PLMI) the monitor requires comparison with the gold standard, PSG. Thus, in Study 2 the research question were:

1. Can the auxiliary EMG channel of the Medibyte® be utilized to accurately record PLMs and what is the degree of agreement between Medibyte PLMI and PSG PLMI?
2. What is the intra-rater reliability for scoring Medibyte® records for PLMI?
3. What is the inter-rater reliability for scoring Medibyte® records for PLMI?

4.2 Introduction & Rationale

4.2.1 Restless Legs Syndrome

Currently, diagnosis of Restless Legs Syndrome is based primarily on subjective reports combined with supporting features. There are 4 essential subjective criteria, primary of which is an urge to move the legs (can be arms) associated with uncomfortable sensations. These symptoms are worse during the evening/night and with inactivity and can sometimes be partially or totally alleviated by movement (Allen, et al., 2003). The unpleasant sensations are typically described as “creepy-crawly”, “jittery”, “worms moving,” “burning”, “itching bones”, “fidgets”, or “electric current”.

48
Other supportive criteria or associated features may include disturbed sleep, periodic limb movements (during waking and/or sleeping), and family history of RLS. To accurately synthesize all of the above, a diagnosis of RLS requires a detailed interview with a trained physician (Trenkwalder, Hogl & Winkelman, 2009).

Given that the only objectively measurable element of RLS is the PLMI (Allen et al., 2003), an accurate, reliable and efficient method of determining this would greatly facilitate the diagnosis and study of RLS. Currently, overnight study in a Sleep Laboratory is the “gold standard” for studying PLMs (Allen, 2007; Trenkwalder, Hogl & Winkelman, 2009). The cost of a one-night sleep study in Ontario is $384 (personal communication, H. Driver, June 2011). Additionally, accessing this service can be difficult; wait times for a sleep study in Ontario vary by centre, but Rotenberg et al (2010) found an average time of 4.9 months from referral. The National Institutes of Health recognized the need for more accessible methods of studying RLS as long ago as 2003, when they called for the development of devices to facilitate convenient methods for measuring PLMs (Allen et al., 2003). The Braebon Medibyte® does hold some promise as a potential method of determining PLMI at home. Costs and wait times could be substantially reduced in comparison to the current standard of in clinic PSG.

4.2.2 The Braebon Medibyte as a potential PLM recording device

There are two questions regarding the validity of the Medibyte® as a valid tool for measuring PLMs. As addressed in Study 1, the sampling frequency of the EMG recording sensor of the Medibyte® is lower than recommended guidelines, both the World Association of Sleep Medicine (WASM) guidelines (Zucconi et al., 2006) of 200Hz for clinical studies and 400 Hz in research studies, and the 1000Hz standard recommended for surface EMG studies by the International Society of Electrophysiology and Kinesiology (ISEK) (DeLuca, 2003). This low sampling rate could cause inaccurate recording of important EMG timing variables (Ives &
Wigglesworth, 2003) of limb movements despite an anti-aliasing filter.

Secondly, EMG recordings of the right and left legs are combined into one recorded channel prior to analysis which is discouraged in the WASM Standards (Zucconi et al., 2006), which state that bilateral recordings are required for research in particular. The impact of this deficiency is a potentially altered detection rate of PLMs (De Luca, 2001). However, PSG studies in the Sleep Laboratory in which this study was conducted also combine both leg channels into one recording.

4.2.3 Reliability of scoring PSG recordings

Research in the area of inter-rater and intra-rater reliability for scoring of PSG recordings has shown mixed results (Whitney et al., 1998, Collop, 2002). Collop (2002) examined inter-rater reliability among 11 PSG technologists working in nine sleep laboratories throughout North America. All centres utilized the same collection software, but no data were obtained on scoring rules in use at each centre. Technologists’ years of experience ranged from three to eleven. Analysis yielded a kappa statistic of 0.31 for total apneas and hypopneas scored for all studies and scorers (Collop, 2002). No significance level or confidence intervals were given. This result indicated only fair agreement between scorers in this study, but the low reliability could be due to multiple factors including varied levels of experience and non-standardized scoring rules and definitions. Among the recommendations of this study were to ensure regular quality management testing of technologists’ scoring within a centre and standardization of PSG scoring rules (Collop, 2002).

In contrast, Whitney et al (1998) found much higher levels of inter-rater reliability with more standardized scoring. They examined reliability during the first stages of the Sleep Heart Health Study (SHHS), during which participants underwent in-home, unattended overnight sleep studies for the screening of OSA. Three PSG technologists, all with the same training, and
experience of having scored at least 80 studies with the standardized criteria (Quan, et al., 1997), scored 20 studies visually for respiratory events (with no EEG data). ICC value for inter-rater reliability in scoring respiratory events was 0.97 (using 3% blood oxygen saturation rule); no confidence interval or significance level was given (Whitney et al., 1998). Intra-rater reliability was examined by t-test. One scorer identified, on average, significantly more respiratory events on their second analysis of the same 20 records; mean difference -0.85 ± 1.26, p < 0.001, whereas the other two did not (Whitney et al., 1998). Further reliability analysis, such as ICC values, with confidence intervals, would provide a clearer picture of the intra-rater reliability for scoring PSG recordings with standardized criteria.

The AASM has produced voluntary Standards for Accreditation of Sleep Disorders Centres (2011) in which they stipulate that inter-rater comparisons must be made between each scorer in a facility and a designated Sleep Specialist on a minimum of 12 PSG recordings per year. Records must be kept on inter-rater reliability for each scorer, though a benchmark value is not suggested.

No studies were identified that examined inter-rater or intra-rater reliability for obtaining a PLMI by PSG or portable monitor, but it is reasonable to postulate that reliability in this task would also be subject to issues of experience and standardization. This is an area that merits further exploration.

4.2.4 Study Objectives

The objectives of this study are to:

1. Determine the validity of PLMI derived from the auxiliary EMG channel of the Medibyte® portable monitor as compared to that obtained through polysomnography (PSG) in a convenience sample of people presenting for in-centre sleep study at the Kingston General Hospital Sleep Laboratory.
2. Determine the intra-rater reliability for scoring the portable monitor recordings to obtain a PLMI.

3. Determine the inter-rater reliability for scoring the portable monitor recordings and obtaining a PLMI.

It is hypothesized that concurrent validity of the Medibyte® portable monitor will be demonstrated through accurate PLM counts from Medibyte recordings in comparison with PSG, and thus validate the portable monitor for use in home measurement of PLMs. Additionally, it is hypothesized that analysis of a subset of recordings will demonstrate good intra- and inter-rater reliability for PLM scoring of Medibyte® recordings.

### 4.3 Methods

#### 4.3.1 Study Design

To explore the reliability of PLMI derived from Medibyte® portable sleep monitor recordings in comparison with PSG, the portable monitor was tested simultaneously with full PSG in overnight sleep studies at Kingston General Hospital (KGH) in patients referred for screening of sleep disorders between November 2010 and February 2012. All studies were scored using the American Academy of Sleep Medicine (AASM) (2007) scoring criteria. Further investigation into the inter-rater and intra-rater reliability for PLM scoring of the Medibyte® recordings was subsequently performed on the recordings obtained for the first study objective.

#### 4.3.2 Instrumentation

4.3.2.1 Polysomnography

Polysomnography (PSG) was conducted with the Sandman SD 32+ Amplifier™ (http://www.embla.com/index.cfm/id/46/SD32-) and included four electroencephalogram channels, two electro-oculogram channels, finger pulse oximetry, nasal/oral flow pressure...
transducer, vibration snore channel, two respiratory effort channels (chest and abdomen), surface electromyography (EMG) channel for bruxism (jaw movement), surface EMG of the intercostal muscles and surface EMG for leg movements (bilateral tibialis anterior) (Figure 4-1). Leg EMG channels consisted of one recording electrode placed over each tibialis anterior muscle on the upper anterior-lateral shin of the patient. The reference electrode was placed over the central midline of the scalp (EEG electrode Cz). (Figure 4-2) The two leg channels were combined to give one tracing on recording. Reusable Grass gold cup electrodes were used with conductive paste and tape adhesive (www.grasstechnologies.com/products/electrodes/electprecintro.html).

Figure 4-1 Polysomnography instrumentation with exception of the nasal cannula (http://www.talkaboutsleep.com/sleep-basics/viewasleepstudy.htm, retrieved May14, 2012)

10-20 electrode placement
Sandman Elite® Sleep Diagnostic Software (version 6.1) is used with the Sandman SD32+ Amplifier™ and all recording channel properties are set in that interface. The data was converted from analog to digital form by an integrated 16 bit AD card. All overnight sleep recordings in this study were collected with a sampling frequency for surface EMG of 128Hz (personal communication, H. Driver March, 2011). Signal filtering consisted of an anti-aliasing filter at 64Hz, high pass filter at 10Hz, low pass at 100 Hz and a 60Hz notch filter (personal communication H. Driver, June 2012). The rationale for low sampling frequencies is to minimize the size of the files that must be stored (personal communication, H. Driver, KGH, May, 2011 & S. Frenette, Centre for Advanced Research in Sleep Medicine, May 2, 2011). There was no post processing of the EMG signal (i.e. rectification or smoothing). The technologist adjusted gain and impedance at the time of the study to maximize the quality of the recording. Impedance was generally kept below 10KOhms.
4.3.2.2 Medibyte® Portable Monitor

The portable monitor used was the Medibyte®, developed by Braebon of Kanata Ontario (http://www.braebon.com/products/medibyte/specs.php, retrieved June 8, 2011, 11:17am) for the home screening of OSA. The Medibyte® device is marketed as a home sleep lab that fits in the palm of your hand. It weighs approximately three ounces, has channels for measurement of respiratory effort (chest and abdomen), blood oximetry, nasal airflow, heart rate, snore audio, body position (3 axis accelerometer), event marker, and auxiliary channels for EMG (Braebon Medical Corporation, 2011) (see Figure 4-3).

![Image](http://www.braebon.com/products/medibyte/index.php, retrieved June 8, 2011, 11:17am)

**Figure 4-3** Medibyte® portable monitor for home screening of Obstructive Sleep Apnea (http://www.braebon.com/products/medibyte/index.php, retrieved June 8, 2011, 11:17am)

Table 4-1 compares the channels and features used in PSG at KGH with those available on the Medibyte® portable sleep monitor.

The Medibyte unit uses a 24bit AD card for conversion of the signals from analog to digital format for processing. The EMG signal (250Hz sampling frequency) is not rectified. There is no low pass filter in the device but there is a 125 Hz anti-aliasing filter. The device has a high pass filter at 0.73 Hz and a notch filter at 60 Hz. The software incorporates a high pass filter
of 10 Hz (personal communication with D. Bradley, Medibyte® developer, June, 2012). Therefore, the device only records frequencies between 0.73 Hz and 125 Hz (even though it is sampling up to 250 Hz). The notch filter removes frequencies at 60 Hz (to eliminate any “noise” on the recording due to nearby electrical equipment). Table 4-2 summarizes the details of surface EMG acquisition specifications for both PSG and the Medibyte® portable monitor.
<table>
<thead>
<tr>
<th>SENSORS</th>
<th>POLYSOMNOGRAPHY (GOLD STANDARD)</th>
<th>MEDIBYTE® (PORTABLE MONITOR)</th>
</tr>
</thead>
<tbody>
<tr>
<td>EEG</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Oximetry</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Heart rate</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Pressure flow</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Snore</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Chest effort</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Abdomen Effort</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Electrocardiogram (EKG)</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Electromyography (EMG)</td>
<td>Jaw + intercostal + tibialis anterior (125Hz sampling rate)</td>
<td>Jaw or tibialis anterior (250 Hz sampling rate)</td>
</tr>
<tr>
<td>Body position</td>
<td>Monitored by video</td>
<td>Built in tri-axial accelerometer</td>
</tr>
<tr>
<td>Ability to monitor signal in real time</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Ability to add information to the recording</td>
<td>Technologist can add comments in real time</td>
<td>Participant/patient can press event button to mark the recording</td>
</tr>
</tbody>
</table>

**Table 4-1** Comparison of PSG and Medibyte® channels/features; Medibyte can record EKG OR EMG, not both at the same time.
Table 4-2 Surface EMG acquisition specifications for both EMG recording systems.

<table>
<thead>
<tr>
<th></th>
<th>SANDMAN SD 32+ AMPLIFIER WITH SANDMAN ELITE DIAGNOSTIC SOFTWARE</th>
<th>MEDIBYTE® ELECTROMYOGRAPHY (EMG) PROCESSOR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sampling frequency</td>
<td>128Hz</td>
<td>250Hz</td>
</tr>
<tr>
<td>Impedance</td>
<td>10GOhms</td>
<td>Not specified</td>
</tr>
<tr>
<td>Rectification</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>Filtering</td>
<td>High Pass – 10 Hz, Low Pass – 100Hz, Anti-aliasing 64Hz, Notch filter- 60Hz</td>
<td>High pass – 10 Hz, Anti-aliasing – 125 Hz, Notch filter – 60 Hz</td>
</tr>
<tr>
<td>Analog-Digital Conversion</td>
<td>16 bit</td>
<td>24 bit</td>
</tr>
<tr>
<td>Common Mode Rejection Ratio</td>
<td>&gt; 100 Db</td>
<td>Not specified</td>
</tr>
</tbody>
</table>

The Medibyte® device preprocesses all the collected EMG data and presents in the form of a tracing through the Pursuit Sleep Software® program. It is unknown how the data is processed. The Medibyte® does offer the ability to monitor respiratory effort, nasal flow and blood oxygen levels, therefore information about respiratory events is available to aid in the scoring of PLMs. There is no information regarding sleep/wake cycles, but the body position sensor in the device does indicate when an individual is standing and therefore movements associated with bathroom visits can be discarded. A PLMI can be derived from the number of movements per hour of recording time, which may or may not be in agreement with a PLMI derived from PSG.

Another consideration in using the Medibyte® device for PLM measurement is the fact that it does present the EMG information as one summed channel for both legs rather than individual channels for each. Summing the channels increases the difficulty in determination of
change in voltage levels for the Medibyte® and may lead to over or under estimation of limb movements. However, the PSG recording system with which the Medibyte® was compared also combines both leg channels as one for the recording.

4.3.4 Participants

A sample of convenience was utilized. Participants (n = 40) in this study were patients referred to the Kingston General Hospital Sleep Laboratory for screening of sleep-related disorders who attended between November 2010 and February 2012.

Inclusion criteria consisted of attendance in the Sleep Lab for a diagnostic or possible split diagnostic/Continuous Positive Airway Pressure (CPAP) titration sleep study and age of 18 years or older. Participants were not considered for inclusion if they would require extra assistance during their diagnostic study (e.g. patients in wheelchairs, with Down’s Syndrome) or would have trouble understanding the purposes of the study (language barrier) sufficiently to provide informed consent.

Informed consent was obtained from each participant by the investigator, after their arrival in the sleep laboratory, prior to being set up for their sleep study (Letter of Information and Consent – Appendix 7.8). Ethics approval for this study was obtained from the Health Sciences Research Ethics Board (Code# DMED-1003-07 Romeo file# 6004601) as part of a larger project that compared this device with PSG for all measures of sleep studies (Appendix 7.9).

4.3.5 Procedures

Participant demographic information was recorded from the Sleep Clinic letter or from the referral if the participants were not seen in the Sleep Clinic prior to their overnight sleep study. This information included age, gender, date of birth and reason for referral. Additionally,
the Epworth Sleepiness Scale was recorded as well as any listed diagnoses and medications. If
the patients were seen in the Sleep Clinic prior to their study, height, weight, BMI and neck
circumference information were also available. Referral procedures were modified over the
duration of this project so many of the latter participants were not seen in Clinic prior to their
study and thus not all of the demographic information was available for all individuals who
participated in this study. Facilities were not available within the Sleep Laboratory itself to
obtain this information at the time of the participant visit.

The PSG Technologist responsible for that patient applied all PSG equipment. A total of
five technologists were involved. Once the PSG equipment was in place, the investigator applied
the portable monitor. Thus the participants wore two additional respiratory effort belts, two
additional EMG electrodes over each tibialis anterior muscle, an extra EMG reference electrode
on the upper left chest, and an extra finger pulse oximeter. The Medibyte® processing unit was
worn on the chest respiratory effort belt (Figure 4-4). Participants only wore one nasal cannula
with the nasal flow signal being split to the PSG and the Medibyte® via a Y connector. This
allowed simultaneous recording of the same flow signal by both monitors.

The Medibyte® device was programmed on the Sleep Lab computers prior to each
participant being set up. This consisted of inputting demographic information and study start
time. Additionally, this ensured that the time of day information on the Medibyte® matched that
on the Sleep Laboratory recording. Synchronizing the two equipment clocks ensured the
subsequent recordings could be accurately matched for timing of events.

The Medibyte® was applied to the participants once they had been set up with the PSG
equipment. Figure 4-4 is a view of the Medibyte® equipment placement for a sleep only study,
while Figure 4-5 shows the addition of the EMG sensors on the legs. Two Medibyte® monitors
were available for this project enabling two participants to be tested at the same time.

60
**Figure 4-4** Medibyte® portable monitor set up for Sleep Apnea screening (Medibyte® Patient Guide, 2010; reproduced with permission.)
Figure 4-5 Medibyte® portable monitor Periodic Limb Movement (PLM) set up (Medibyte® Patient Guide, 2010; reproduced with permission.)

4.3.5.1 Periodic Limb Movement Index (PLMI) Scoring

4.3.5.1.1 American Academy of Sleep Medicine Guidelines for Scoring of Sleep Studies

All PSG and Medibyte® recordings were scored according to American Academy of Sleep Medicine guidelines. These are standardized methods for recording and scoring PLMs in sleep (AASM, 2007).

“A. The following rules define a significant leg movement (LM) event:
1) The minimum duration of a LM event is 0.5 seconds.
2) The maximum duration of a LM event is 10 seconds
3) The minimum amplitude of a LM event is an 8µV-increase in EMG voltage above resting EMG.
4) The timing of the onset of a LM event is defined as the point at which there is an 8µV-increase in EMG voltage above resting EMG.

5) The timing of the ending of a LM event is defined as the start of a period lasting at least 0.5 seconds during which the EMG does not exceed 2µV above resting EMG.

B. The following rules define a PLM series:

1) The minimum number of consecutive LM events needed to define a PLM series is 4 LMs.

2) The minimum period length between LMs (defined as the time between onsets of consecutive LMs) to include them as part of a PLM series is 5 seconds.

3) The maximum period length between LMs (defined as the time between onsets of consecutive LMs) to include them as part of a PLM series is 90 sec.

4) Leg movements on 2 different legs separated by less than 5 seconds between movement onsets are counted as a single leg movement.

Notes:

1. A LM should not be scored if it occurs during a period from 0.5 seconds preceding an apnea or hypopnea to 0.5 seconds following an apnea or hypopnea.

2. An arousal and a PLM should be considered associated with each other when there is <0.5 seconds between the end of one event and the onset of the other event regardless of which is first.

3. Surface electrodes should be placed longitudinally and symmetrically around the middle of the muscle so that they are 2 to 3 cm apart or one third of the length of the anterior tibialis muscle, whichever is shorter. Both legs should be monitored for the presence of the leg movements. Separate channels for each leg are strongly preferred. Combining electrodes from the two legs to give one recorded channel may suffice for some clinical settings, though it should be recognized that this strategy may reduce the number of detected LMs. Movements of the upper limbs may be sampled if clinically indicated.

4. The rules in “A” above define a significant leg movement event by absolute increase in µV above resting baseline for the anterior tibialis EMG. This requires a stable resting EMG for the relaxed anterior tibialis whose absolute signal should be no greater than +10µV between negative and positive deflection (±5 µV) or +5 µV for rectified signals.

5. Use of 60 Hz (notch filters) should be avoided. Impedances need to be less than 10,000Ω. Less than 5,000Ω is preferred but may be difficult to obtain. Sensitivity limits of -100 and 100µV (upper/lower) are preferred.”

(AASM Manual for Scoring Sleep, 2007, p. 41)

To summarize, bursts of muscle activity (greater than 8µV above baseline EMG voltage) on the PSG recording can only be considered a possible PLM if the EMG burst does not occur within 0.5 seconds of the start or end of a breathing event, if the EMG burst has duration of between 0.5 and 10 seconds, if there are at least 0.5 seconds between offset of one EMG burst and the start of the next, if there is a duration of onset of one burst to onset of the next of not less than 5 seconds and not more than 90 seconds, and if the EMG bursts meeting these criteria occur in a series of at least four (4).
4.3.5.1.2 Periodic Limb Movement Index (PLMI) Scoring - PSG recordings

Recording start time was set on the Medibyte® when it was programmed (on the evening of the sleep study) while PSG recording started once the participant was in bed. If the PSG began earlier than the start time on the Medibyte® (e.g. participant decided to go to bed earlier) – the Medibyte® potentially missed PLMs captured by the PSG. Conversely, if the Medibyte started early® (e.g. participant went to sleep much later) its recording will capture calibration movements prior to the start of PSG scoring that cannot be ruled out because there is no EEG recording and therefore no sleep/wake information. This was accounted for by ensuring the scoring start times for each participant matched between PSG and Medibyte® recordings.

One experienced analyst (H.D.) scored all PSG recordings. Breathing events (apneas & hypopneas) were identified based on AASM 2007 (alternative) criteria. For the purpose of scoring a sleep study recording, an apnea is defined as a complete or near complete cessation (90% decrease) of airflow for at least ten seconds, followed by an arousal and/or 3% oxygen desaturation. A hypopnea is defined as 50% decrease in the airflow signal followed by an arousal or 3% oxygen desaturation (AASM, 2007).

Numbers of limb movements meeting the AASM 2007 criteria as outlined above were counted for the total recording time whether the patient was asleep or awake. Voltage information for the EMG recording was viewed to verify that the increase in voltage qualified as a limb movement. Voltage lines applied to the tracing at the 8µV above and below the calibrated resting level of EMG voltage allowed identification of all muscle activity extending beyond these lines as candidate limb movements.

Candidate limb movements meeting the above criteria were scored regardless of whether the individual was awake or asleep during the movements. A PLMI of the number of PLMs per hour of recording time was obtained from each PSG study.
**Figure 4-6** 20 second screenshot of a PSG tracing (PLM03)

EMG of the legs is shown on the middle channel (purple). The transparent boxes (green) over the airflow signal channel (blue) show periods of apnea or hypopnea. The oxygen saturation values are shown numerically at the bottom of the recording with (black) transparent boxes above to mark relative desaturation.

4.3.5.1.3 Periodic Limb Movement Index (PLMI) Scoring - Medibyte® recordings

Medibyte® studies were scored by the principal investigator (M.J.O’D.) according to the same criteria as described above for the PSG (AASM Manual, 2007), and a PLMI was similarly obtained.
Surface EMG channel for the legs are the top tracing. Muscle activity bursts have been highlighted in green. Apneas/Hypopneas are highlighted in yellow over the flow signal and summed respiratory effort channel. The blue highlight signifies a blood oxygen desaturation of 3% or greater.

Voltage information on the Medibyte® recordings was available as minimum, maximum and range values for a highlighted portion of the recording. Thus, the exact point where 8µ deflection from baseline starts is not specifically pinpointed by the software (Figure 4-8). The onset of limb movement activity was determined visually by inspection of the tracing in a 30 second window. A candidate limb movement was highlighted, as was an equal portion of the baseline shortly before the event. The range value for each highlighted portion was compared to ensure that this value was at least 16µ greater for the limb movement section. The 16µ value was chosen to ensure that there was a minimum 8µ deflection in one direction from the baseline. This
had to be done for virtually every candidate limb movement, as the baseline voltage range could be quite variable.

Figure 4-8 Screenshot of a 30 second section of a Pursuit sleep study
Green highlighted section is a limb movement with voltage information shown in the inset box.

A notable difference between recordings obtained by Medibyte® and by PSG was the lack of EEG information on the Medibyte®. Thus, with the Medibyte®, no sleep stage information is available to determine whether limb movements occur while an individual is awake or asleep. Therefore to allow a more accurate comparison between PLM counts by both
systems, all limb movements meeting the above criteria were counted in the PSG studies regardless of occurring in sleep or waking.

In studies in which the diagnostic portion was terminated and Continuous Positive Airway Pressure (CPAP) titration started part way through the night (“split night studies”), only the diagnostic portion of the recordings was scored for limb movements. The nasal cannula is removed during CPAP titration as the patient wears a CPAP mask during the titration. This results in a lack of airflow information on the Medibyte® during the CPAP titration portion of the study, which means breathing events cannot be scored. Therefore, limb movements associated with apneas or hypopneas cannot be excluded from the total count, resulting in an inaccurate PLMI.

4.3.5.2 Intra- & Inter-rater Reliability of scoring PLMI derived from Medibyte®

Intra-rater reliability for obtaining a PLMI with the Medibyte® was examined. The study investigator (M.J.O’D.) re-scored a random sample of eighteen of the Medibyte® recordings obtained during the validation protocol. The re-scoring was performed after all sleep studies had been completed and three to twelve months after the original scoring of the studies was done. Blinding to the original score was achieved due to the time elapsed between first and second scoring.

Inter-rater reliability for scoring the MB recordings was also explored in a small subsample of 5 randomly chosen recordings. An experienced (H.D.) and a novice (M.J.O’D.) analyst each completed PLMI scoring independent of each other and blinded to the others’ score.

4.3.6 Data Analysis

The resulting PLMI values for each participant were examined for outliers (Z-scores) and normal distribution (skewness/kurtosis values and Kolmogrov-Smirnov test). The PLMI values
for each method were analyzed by paired t-test to compare means. Correlation of the two sets of values was tested using Pearson correlation coefficient and by the Intraclass Correlation Coefficient (ICC) using a two-way random effects, single measures model for absolute agreement (Model 2,1 – Weir, 2005, Shrout & Fleiss, 1979). The degree of agreement between the two PLMI values for each participant was explored with a Bland-Altman plot (Bland & Altman, 1986, 2003).

Intra- and inter-rater reliability were tested with paired t-tests to compare means and determine a mean difference in values. Pearson’s r values and ICC (2,1) values were calculated to determine correlation between scores for both intra- and inter-rater reliability.

Correlation coefficients will be classified according to Currier’s recommendations (1990, as cited in Ko, Han, Cho & Lee, 2010), where 0.69 or less is considered poor, 0.70 to 0.79 is fair, 0.80 to 0.89 is good and 0.90 and above is high reliability.

4.4 Results

Of the 40 participants, 19 were male (47.5%) and 21 were female (52.5%). Participant age ranged from 28 to 75 years of age with an average age of 54.8 ± 13.0. Reasons for referral to the sleep laboratory included obstructive sleep apnea, narcolepsy, and insomnia. Participants also had a wide range of co-morbidities including hypertension, diabetes, irritable bowel syndrome, asthma, obesity, fibromyalgia, depression, arthritis, arrhythmia, post-traumatic stress disorder, myocardial infarction, ischemic heart disease, atherosclerosis, hyper-cholesteremia, diverticulosis, chronic renal failure, bipolar disorder, osteoporosis, peripheral neuropathy, hypothyroidism, breast cancer, malignant melanoma, sciatica, Parkinson’s Disease, and Raynaud’s syndrome. One individual (PLM 34) was diagnosed with Restless Legs Syndrome and was taking medication for this (Mirapex). Several others (PLM07, 10, 14, 30, 35) indicated subjective features suggestive of RLS such as “heebie jeebies” in the legs, and leg twitches and
discomfort that disturbed sleep. Weight and height information was available for 28 and 16 participants respectively and BMI was available on 25 participants. Average weight from the available data was 90.4kg, average height, 167.5cm and BMI, 31.5 kg/m². Participant demographics are summarized in Table 4-3.

<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th>MEAN ± SD</th>
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<tbody>
<tr>
<td><strong>Age</strong></td>
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<td>54.8 ± 13.0</td>
<td>27.6 – 75.0</td>
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<tr>
<td><strong>Gender (Male:Female)</strong></td>
<td>40</td>
<td>19:21</td>
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</tr>
<tr>
<td><strong>Weight</strong></td>
<td>28</td>
<td>90.4kg ± 19.9kg</td>
<td>53kg – 162.4kg</td>
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<tr>
<td><strong>Height</strong></td>
<td>16</td>
<td>167.5 cm ± 10.6cm</td>
<td>153cm – 184cm</td>
</tr>
<tr>
<td><strong>BMI</strong></td>
<td>25</td>
<td>31.5 kg/m² ± 4.8kg.m²</td>
<td>23.5kg/m² – 42.7kg/m²</td>
</tr>
</tbody>
</table>

**Reasons for Referral:**

<p>| | | | |</p>
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<thead>
<tr>
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<td><strong>Sleep Apnea</strong></td>
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<td>N/A</td>
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<td>N/A</td>
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<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td><strong>Other</strong></td>
<td>3</td>
<td>N/A</td>
<td>N/A</td>
</tr>
</tbody>
</table>

**Table 4-3** Summary of patient demographics; N= number, SD = standard deviation

Of the 40 participants, only 35 overnight sleep recordings resulted in data that could be analyzed. One participant asked to have the portable monitor removed within one half hour of starting the study. Another four recordings had technical problems including a faulty battery that resulted in no overnight recording for one participant, another recording that had no oximetry
signal, and two others with such poor quality nasal flow signals that the recordings could not be scored reliably for breathing events.

Of the analyzed recordings, 11 were split-night studies, so had durations of between 120 minutes to 305 minutes (mean = 225 ± 58 minutes). Full night studies (24) had durations ranging from 297 minutes (participant asked to have the monitor removed partway through the night) to 541 minutes (mean = 429 ± 60 minutes).

A poor quality flow signal in six Medibyte® recordings created challenges in scoring for breathing events in these studies and was a possible source of error. The oximetry signal was intermittent in some studies. The sections of Medibyte® recording without an oximetry signal were marked as bad data and were not included in the scoring. The two portable monitors were labeled and it was documented which was used in which study. There was not a consistent pattern as to which monitor had more loss of the oximetry signal. This could also be a source of error causing some of the variability between PLMI values.

4.4.1 Validity of PLMI determined by Medibyte® versus by PSG

Analysis of Z scores determined that there were no data points greater than 3 standard deviations above or below the mean value for each set of PLMI values. The PSG and Medibyte® PLMI data were not normally distributed; Kolmogorov–Smirnov test showed $D(35) = 1.9$, $p < 0.05$ for the PSG PLMI and $D(35) = 1.9$, $p < 0.05$ for the Medibyte PLM data. Skewness values for PSG PLMI = 1.42, for Medibyte® PLMI = 1.12; kurtosis values were 1.3 and .78. Values for skewness approaching one or above indicate the data is clustered in either the upper or lower range (Field, 2009). The higher the kurtosis value, the flatter the distribution of values in a data set. Transformation of the data improved these characteristics only slightly so data analysis proceeded with the original data. The issue of the non-normal distribution of the PLMI values was expected. Given that less than 20% of the population is expected to have PLMs, the majority
of participants in this study sample should have PLM Indices of 11 or below. Many studies using PLMI as a measure proceed with parametric data analysis, with or without data transformation, despite a non-normal data distribution (Esteves et al., 2008; Oertel et al., 2010).

PSG and Medibyte® PLMI values for each participant are shown in Table 4-4.

<table>
<thead>
<tr>
<th>PARTICIPANT#</th>
<th>PLMI MEDIBYTE®</th>
<th>PLMI PSG</th>
<th>DIFFERENCE</th>
<th>SPLIT NIGHT</th>
</tr>
</thead>
<tbody>
<tr>
<td>PLM01</td>
<td>monitor removed</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>PLM02</td>
<td>27</td>
<td>8.3</td>
<td>18.7</td>
<td>-</td>
</tr>
<tr>
<td>PLM03</td>
<td>36.7</td>
<td>15</td>
<td>21.7</td>
<td>Split</td>
</tr>
<tr>
<td>PLM04</td>
<td>12.5</td>
<td>2.3</td>
<td>10.2</td>
<td>-</td>
</tr>
<tr>
<td>PLM05</td>
<td>16</td>
<td>0</td>
<td>16</td>
<td>-</td>
</tr>
<tr>
<td>PLM06</td>
<td>6.5</td>
<td>0.9</td>
<td>5.6</td>
<td>-</td>
</tr>
<tr>
<td>PLM07</td>
<td>3.5</td>
<td>0.6</td>
<td>2.9</td>
<td>-</td>
</tr>
<tr>
<td>PLM08</td>
<td>Faulty battery</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>PLM09</td>
<td>19.6</td>
<td>9.5</td>
<td>10.1</td>
<td>-</td>
</tr>
<tr>
<td>PLM10</td>
<td>43.5</td>
<td>21.8</td>
<td>21.7</td>
<td>Split</td>
</tr>
<tr>
<td>PLM11</td>
<td>60.7</td>
<td>20.7</td>
<td>40</td>
<td>Split</td>
</tr>
<tr>
<td>PLM12</td>
<td>36.8</td>
<td>10.5</td>
<td>26.3</td>
<td>Split</td>
</tr>
<tr>
<td>PLM13*</td>
<td>3.4</td>
<td>11.3</td>
<td>-7.9</td>
<td>Split</td>
</tr>
<tr>
<td>PLM14*</td>
<td>6.9</td>
<td>8</td>
<td>-1.1</td>
<td>--</td>
</tr>
<tr>
<td>PLM15</td>
<td>1.5</td>
<td>0</td>
<td>1.5</td>
<td>-</td>
</tr>
<tr>
<td>PLM16</td>
<td>Poor flow signal</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>PLM17</td>
<td>15</td>
<td>12.7</td>
<td>2.3</td>
<td>-</td>
</tr>
<tr>
<td>PLM18</td>
<td>1.6</td>
<td>0</td>
<td>1.6</td>
<td>Split</td>
</tr>
<tr>
<td>PLM19</td>
<td>Poor flow signal</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>PLM20</td>
<td>No oximetry signal</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>PLM21*</td>
<td>8.64</td>
<td>12.9</td>
<td>-4.26</td>
<td>Split</td>
</tr>
<tr>
<td>PLM22</td>
<td>6.4</td>
<td>4.1</td>
<td>2.3</td>
<td>-</td>
</tr>
<tr>
<td>PLM23</td>
<td>34.1</td>
<td>18.4</td>
<td>15.7</td>
<td>Split</td>
</tr>
<tr>
<td>PLM24*</td>
<td>8.5</td>
<td>25.9</td>
<td>-17.4</td>
<td>--</td>
</tr>
<tr>
<td>PLM25</td>
<td>64.6</td>
<td>57.3</td>
<td>7.3</td>
<td>-</td>
</tr>
<tr>
<td>PLM</td>
<td>1.8</td>
<td>0.5</td>
<td>1.3</td>
<td>-</td>
</tr>
<tr>
<td>-------</td>
<td>-----</td>
<td>-----</td>
<td>-----</td>
<td>-----</td>
</tr>
<tr>
<td>PLM26</td>
<td>8.5</td>
<td>13</td>
<td>-4.5</td>
<td>Split</td>
</tr>
<tr>
<td>PLM27*</td>
<td>67.2</td>
<td>71.9</td>
<td>-4.7</td>
<td>Split</td>
</tr>
<tr>
<td>PLM28*</td>
<td>16</td>
<td>5</td>
<td>11</td>
<td>-</td>
</tr>
<tr>
<td>PLM29</td>
<td>27.2</td>
<td>21.3</td>
<td>5.9</td>
<td>-</td>
</tr>
<tr>
<td>PLM30</td>
<td>43.9</td>
<td>18.5</td>
<td>25.4</td>
<td>-</td>
</tr>
<tr>
<td>PLM31</td>
<td>7.6</td>
<td>17.8</td>
<td>-10.2</td>
<td>-</td>
</tr>
<tr>
<td>PLM32*</td>
<td>29.3</td>
<td>19.3</td>
<td>10</td>
<td>Split</td>
</tr>
<tr>
<td>PLM33</td>
<td>54.8</td>
<td>33.1</td>
<td>21.7</td>
<td>-</td>
</tr>
<tr>
<td>PLM34</td>
<td>41.7</td>
<td>43.2</td>
<td>-1.5</td>
<td>-</td>
</tr>
<tr>
<td>PLM35*</td>
<td>5.3</td>
<td>0</td>
<td>5.3</td>
<td>-</td>
</tr>
<tr>
<td>PLM36</td>
<td>88.2</td>
<td>67.1</td>
<td>21.1</td>
<td>-</td>
</tr>
<tr>
<td>PLM37</td>
<td>2.3</td>
<td>0</td>
<td>2.3</td>
<td>-</td>
</tr>
<tr>
<td>PLM38</td>
<td>1.2</td>
<td>0</td>
<td>1.2</td>
<td>-</td>
</tr>
<tr>
<td>PLM39</td>
<td>1.5</td>
<td>0</td>
<td>1.5</td>
<td>-</td>
</tr>
<tr>
<td>PLM40</td>
<td>88.2</td>
<td>67.1</td>
<td>21.1</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>2.3</td>
<td>0</td>
<td>2.3</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>1.2</td>
<td>0</td>
<td>1.2</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>1.5</td>
<td>0</td>
<td>1.5</td>
<td>-</td>
</tr>
</tbody>
</table>

Table 4-4 Periodic Limb Movement Index (PLMI) values from Polysomnography (PSG) and from Medibyte®; split night = recordings in which CPAP titration began partway through the night, thus ending the Medibyte® collection before the end of PSG

* Studies in which PSG PLMI was greater than Medibyte® PLMI

4.4.1.1 Correlation of PLMI values

Mean Medibyte® PLMI for the 35 studies analyzed was 22.9 ± 22.6. Mean PSG PLMI was 18.1 ± 21.1. The mean difference between the two PLMI values was +4.8 ± 11.1, t (34) = 2.6, p < 0.05, which was statistically significant and demonstrated systematic over-reporting by the portable monitor. As expected, the Medibyte® PLMI and the PSG PLMI were well correlated, giving a Pearson’s r = .87, p < 0.001. Figure 4-9 is a plot of the values with a trend line showing the correlation. The ICC (2,1) value of 0.87 (95% CI, 0.76 - 0.93), p < 0.01 demonstrated statistically significant and good correlation of the Medibyte® PLMI as compared to PSG PLMI.
Figure 4-9 Correlation of Periodic Limb Movement (PLM) Index from Medibyte® with Polysomnography (PSG) PLMI. Vertical lines represent cut-off values for RLS diagnosis (15) and PLMD diagnosis (25).

4.4.1.2 Full night versus split night studies

The results were further analyzed according to full night versus split night. Mean PLMI for the Medibyte® for full night studies was $20.3 \pm 22.8$; for PSG full night studies, $14.0 \pm 18.8$. The mean difference between methods of PLMI measurement for full night studies ($n=24$) was $6.3 \pm 9.1$, which was significantly different ($t(23) = 3.39$, $p < 0.003$). The PLMI values showed high correlation with Pearson’s $r = .92$, $p < 0.01$ and good correlation with an ICC (2,1) value of 0.87 (95% CI 0.6 – 0.95).
Mean PLMI for the Medibyte® for split night studies was 28.52 ± 21.95, for PSG split night studies, 28.65 ± 23.75. The mean difference between portable monitor split night studies (n = 11) and PSG split night studies was only -0.14 ± 16.47. This was not statistically significant (t (10) = -0.27, p > 0.05). Correlation for PLMI determined by the two methods during split night studies was r = 0.74, p < 0.01. ICC (2,1) was 0.74 (95% CI 0.29 – 0.92).

4.4.1.3 Bland-Altman agreement analysis

Absolute agreement between Medibyte® & PSG PLMI values was examined with a Bland-Altman plot (see Figure 4-10). This shows the average PLMI value for each participant plotted against the difference in the two PLMI values for the same participant. The variability between the two PLMI values is quite wide in some instances, with 95% limits of agreement in PLMI being +27.9 (95% CI +33.0 to 20.2) to – 19.3 (95%CI -10.6 to -23.4).
Figure 4-10 Bland-Altman plot. Red line represents the mean difference between PLMI for both measurement tools and green lines represent upper and lower limits of agreement. MB = Medibyte®; PSG = Polysomnography; PLM = Periodic Limb Movement; PLMI = Periodic Limb Movement Index.

4.4.2 Intra-rater reliability

The mean PLMI value obtained for the re-scoring of the 18 recordings (16.9 ± 20.7) was statistically different from the first, being 3.2 ± 4.6 (t = 3.02 (17), p < 0.05) lower. However, Pearson correlation between the two sets of scores was high; r = .98, p < 0.001. Reliability was also high with an ICC (3,1, absolute agreement) of 0.97 (95% CI, 0.86 – 0.99) p < .001.

4.4.3 Inter-rater reliability

The mean difference in PLMI obtained by each scorer was 4.2 ± 4.6, t = 2.05(4), p > 0.05. This difference was not statistically significant. Correlation between the two raters’ scores was high; r= .93, p < .05. ICC (2,1, absolute agreement) value for reliability was fair at 0.78 (95% CI, 0.008 – 0.973), p < 0.05.
Reliability statistics are summarized in Table 4-5.

<table>
<thead>
<tr>
<th></th>
<th>MEDIBYTE®/PSG AGREEMENT</th>
<th>INTRA-RATER RELIABILITY</th>
<th>INTER-RATER RELIABILITY</th>
<th>MEDIBYTE®/PSG AGREEMENT 2ND ANALYSIS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean difference between PLMI values</td>
<td>+4.8 ± 11.1, p &lt; 0.05</td>
<td>-3.2 ± 4.6, p &lt; 0.05</td>
<td>+4.2 ± 4.6, p &gt; 0.05 (NS)</td>
<td>+3.2 ± 11.1, p = 0.10 (NS)</td>
</tr>
<tr>
<td>Pearson’s Correlation</td>
<td>r = .87, p &lt; 0.001</td>
<td>r = .98, p &lt; 0.001</td>
<td>r = .93, p &lt; .05</td>
<td>r = .87, p &lt; 0.001</td>
</tr>
<tr>
<td>Intraclass Correlation Coefficient (2,1)</td>
<td>0.87, (95% CI, 0.76 – 0.93), p &lt; 0.001</td>
<td>0.97 (95% CI, 0.88 – 0.99), p &lt; .001</td>
<td>0.78 (95% CI, 0.008 – 0.973), p &lt; 0.05</td>
<td>0.87, (95% CI, 0.75 – 0.93), p &lt; 0.001</td>
</tr>
</tbody>
</table>

Table 4-5 Summary of results of statistical analysis of the PLMI by Medibyte® vs. PLMI by PSG; PLMI = Periodic Limb Movement Index, NS = not significant.

4.5 Discussion

4.5.1 Key Findings

Results of this study demonstrate good correlation and degree of agreement for obtaining PLMI with the Medibyte® when compared to the current gold standard, PSG. This is to be expected as both methods are measuring the same parameters. This supports the criterion/concurrent validity (Portney & Watkins, 2009) of the Medibyte® for obtaining a PLMI. Reliability between the two methods, as shown by ICC (2,1) value of 0.87, is also good, further supporting the validity of this device for obtaining a PLMI in an overnight sleep study.

Intra-rater reliability for the 18 randomly chosen studies that were scored a second time (with blinding to the initial scores) was very high – 0.97 (95 % CI 0.88 -0.99) demonstrating good consistency in applying the scoring rules by the principal investigator (M.J.O’D.) over time and
between early and later recordings. Intra-rater reliability for this individual does not seem to be a source of error in this study.

Inter-rater reliability for scoring Medibyte® recordings for PLMI was examined in a small subsample (with investigators blinded to each others’ scores). The mean difference between each investigator’s PLMI scores was not statistically significant. The Pearson correlation between PLMI values was high (r = 0.93), indicating that consistency for applying the standardized scoring criteria was good between investigators despite the relative inexperience of the principal investigator in scoring sleep recordings. However, this Pearson r-value might be an overestimation. The ICC value, which accounts for absolute as well as relative reliability, is a better measure in this case (Carter, Lubinsky & Domholdt, 2011). The ICC was fair with a value of 0.78 (95% CI 0.008 – 0.973).

4.5.2 PLMI Over-reporting by the Medibyte®

The portable monitor recordings demonstrated systematic over-reporting of PLMI by approximately five limb movements per hour overnight in comparison to PSG (mean difference 4.8 ± 11.14). This was expected due to the finding that the Medibyte® under-reports respiratory events (Driver et al., 2011). The under-reporting is due to the inability to recognize respiratory effort-related arousals on the Medibyte® recordings. If the recording did not demonstrate the required oxygen desaturation to identify a breathing event, but did have an arousal related to increased respiratory effort, a hypopnea would be scored on the PSG. A breathing event such as this would not be scored on the Medibyte® recording, as there is no arousal (EEG) information. If there were limb movements associated with such a breathing event, those movements would be included in the total limb count on the portable monitor recording (providing they met the other
criteria), but not on PSG. In an individual who had many such respiratory events the PLMI could be substantially higher on the portable monitor recording.

Limb activity monitors demonstrate the same issues with over-reporting of limb movements and thus higher PLMI values when tested against PSG (Allen, 2007a; Sforza, Johannes, & Claudio, 2005; Van de Water, Holmes & Hurley, 2011; Gschliesser et al., 2009). However the over-reporting is significantly higher than found with the portable sleep monitor in the current study. Gschliesser et al., 2009 found that the PAM-RL® over-reported PLMI by a mean of 12.7 ± 11.8 when used on one leg and by 26.6 ± 20.5 if used bilaterally. In comparison, the Medibyte® over-reporting is only 3.2 ± 11.1. The presence of OSA impacts Medibyte® accuracy much less than a limb activity monitor due to the respiratory and oxygen saturation information.

The good correlation PLMI between Medibyte® and PSG held whether the studies were full or split night. The split night studies, which were fewer, had a much smaller mean difference than all the studies taken as a whole. However, this mean difference was negative instead of positive indicating that for studies with high numbers of breathing events, scoring of the Medibyte® recording actually resulted in a slighter lower average PLMI than PSG. This is in contrast to the systematic over-reporting noted when all the studies were analysed together. This effect also resulted in slightly lower correlation between PLMI values and a lower ICC than for all 35 recordings. These results would seem to indicate that in the presence of OSA (i.e. many breathing events), it is more challenging to obtain a reliable PLMI.

### 4.5.4 Absolute agreement

The Bland-Altman analysis provides the most in depth examination of the agreement between PLMI values for each participant. The limits of agreement between the two PLMI
values are quite wide, indicating that despite good correlation and reliability there was at times significant variation between the two devices. Additionally there were eight recordings in which the Medibyte® derived PLMI was lower than that from PSG, contrary to the usual trend (see Table 4-3). This occurrence was not limited to only one of the portable monitors so could not be explained by differences in hardware.

It is logical to explore variances in some aspect of scoring to explain this anomaly in those studies. However, the PLMI in these particular studies was not confined to a specific range of values (i.e. only higher or lower PLMI values) nor was it related to being a split-night study; only four of the eight that demonstrated under scoring by the portable monitor were split-nights.

In the validation study of the Medibyte for screening of OSA (Driver et al., 2011), mean difference and limits of agreement between the monitor and PSG for obtaining a Respiratory Disturbance Index (RDI) were expressed in percentages as well as absolute differences. The mean percentage difference from PSG Apnea- Hypopnea Index was -19%, with limits of agreement of 61% to -99%. Examining the PLMI results in this same way gives a mean difference between Medibyte® PLMI and PSG PLMI of 65.1% with limits of agreement of +158.3% to -28.1%. However this range is very strongly skewed by nine recordings with the lowest PSG PLMI (all < 1.0) where the matching Medibyte® PLMI ranged from 1.6 – 6.1. The percentage mean differences in PLMI in these studies ranged from 110% to 200% with most of them being 200%. Clinically though, the absolute difference between these PLMI (1.6 – 5.6) would not necessarily be significant, as the lowest cut-off for supporting a diagnosis of RLS is 11 (Montplaisir et al., 1998).

4.5.5 Potential Sources of Error

4.5.5.1 Arousal information on the portable monitor recording
One factor that could contribute to divergence between the two methods in some participants was the lack of arousal information on the Medibyte® recording, leading to scoring of leg movements that may have occurred when the participant experienced a respiratory effort related arousal. A limb movement such as this would not be counted as a PLM when scoring PSG. An attempt was made to partially account for this by counting all candidate limb movements on the PSG recording whether in sleep or waking. However, movements associated with hypopneas that caused an arousal, but not a blood oxygen desaturation, would still be scored on the Medibyte® recording.

In a population of patients referred specifically for screening of RLS, the incidence of OSA may be much lower than in this study, which consisted mostly of participants with suspected OSA. The frequent breathing events and associated limb movements that occur with OSA certainly complicate scoring for true PLMs. RLS screening with the Medibyte® overnight could potentially be much more straightforward in individuals without OSA, though the two conditions may co-exist (Allen, 2007a).

4.5.5.2 Lack of real time monitoring

Another potential source of error is the inability to monitor the Medibyte® recording and make corrections. The PSG is monitored in real time, the Medibyte® is not. PSG technologists can observe and correct any recording problems. With the Medibyte® if a signal is of poor quality or a sensor connection becomes faulty it cannot be corrected resulting in the potential for poor quality recordings. Additionally, with technologist attended PSG, timed notes can be documented on the PSG recording that can provide important information for later scoring. The Medibyte® recording cannot be accessed until the study is done and downloaded.

4.5.5.3 Splitting of nasal flow signal
Splitting the nasal flow signal occasionally caused difficulties noted on the real time PSG recording, which prompted the technologists to adjust the Y connector attaching the tubing from the nasal cannula to the two pressure transducers. It is suspected that this may have been the cause of poor flow signals in some Medibyte studies. Unfortunately, as the Medibyte recording is not monitored in real time, this would not be detected until the recording was downloaded after the study was complete. If this was the cause of poor flow signals on the Medibyte® recordings, then poor flow signals may be of less concern with Medibyte® recordings that are done not simultaneously with PSG.

4.5.5.4 EMG electrode placement

It is possible that the slightly different location of the PSG and Medibyte® surface EMG electrodes on the bilateral tibialis anterior muscles had an impact on EMG detection in these studies. With the PSG electrode being placed first, the Medibyte® electrodes may not have always been optimally placed to get the best EMG signal. Additionally because two different sets of electrodes were used on each muscle, the exact same EMG signal would not be collected by both methods (De Luca, 2003). Campanini et al (2007) demonstrated that characteristics of the EMG signal of lower limb muscles could vary significantly dependent on electrode position over the muscle belly. In particular, they noted that for tibialis anterior, a shift of 2-3 centimetres in electrode location could cause as much as 30% variation in signal characteristics. The mean variability ratio (similar to coefficient of variation) was 17% ± 6% (Campanini et al., 2007) between nine electrode channels placed in a four by three grid over the tibialis anterior muscle. In the current study this effect may have a larger or smaller significance in some participants due to their lower leg morphology (i.e. size of the muscle).

4.5.6 Efficacy/Utility of the MB
The portable monitor appeared to be well tolerated by virtually all participants. Most participants were undergoing their first sleep study so all the equipment was novel to them. The addition of a few extra sensors was generally not a concern. This portable monitor would likely be well tolerated in a home setting and this would perhaps give a more representative picture of a “normal” night’s sleep in a non-clinic setting.

4.5.7 Study Limitations & Future Directions

The use of the Medibyte® portable sleep monitor for obtaining a PLMI still has further evaluation to undergo. This study examined Medibyte® reliability in a general population referred for screening of sleep disorders that did not necessarily include RLS, but was focused on breathing or other sleep dysfunctions. Ideally, the Medibyte® should be tested versus PSG in an RLS population that does not also have possible sleep apnea, in order to minimize scoring variability by reducing the problem of over-reporting due to undetected breathing events on the portable monitor recording. This would give a more direct comparison of just the PLM counts between methods. In reality it may not be possible to isolate a participant sample with these characteristics.

Further studies with some design modifications to decrease sources of error should show tighter absolute agreement between these two methods. Those modifications could include better coordination of electrode placement between the two systems or utilization of one set of electrodes and splitter connections as per Study 1, dedicating one PSG technologist to study participant setup, and having scoring completed by analysts with similar experience levels.

The Medibyte® should be validated in special populations that have RLS secondarily to determine whether their primary condition (e.g. End-Stage Renal Disease undergoing hemodialysis, Chronic Obstructive Pulmonary Disease) has particular considerations that affect
the reliability of the device and/or the its efficacy for PLM measurement (Winkelman, Chertow, & Lazarus, 1996; Kaplan, Inonu, Yilmaz & Ocal, 2008).

Given the fact that the portable monitor appears to over-report the PLMI vs. PSG, this would affect the cut-off for supporting diagnosis of RLS using this device. A study designed to evaluate sensitivity and specificity for determining accurate PLMI in support of RLS diagnosis with the Medibyte® is warranted.

4.6 Conclusion

It is concluded that the Medibyte® portable sleep monitor demonstrated significant reliability in comparison to the gold standard, PSG, for obtaining a PLMI, in a participant population with a variety of sleep disorders. This supports the validity of the device for determining a PLMI in RLS patients, either for supporting diagnosis or as a measure of change. If further testing of this device continues to uphold this validity, the Medibyte® could be utilized as a more convenient and efficacious substitute for the current gold standard, PSG, for determining PLMI.
Chapter 5

Discussion

5.1 Key Findings of the Research

While there may be some question of the validity of the Medibyte® EMG channel for collecting surface EMG data related to sampling frequency, based on the ability to accurately record numbers of muscle contractions, the Medibyte® does have concurrent validity with standard surface EMG for this purpose (Study 1). Medibyte® EMG collection parameters are similar to PSG EMG collection system at Kingston General Hospital (Study 2). For determining a PLMI, the Medibyte® shows good agreement with the gold standard, PSG, and could serve as a substitute measure. A strong case can be made for concurrent validity of the Medibyte® for determining PLMI with PSG based on the results of Study 2. This validity held whether the studies were full or split night. In practice using this device at home, the studies would be full night. However, unless OSA is ruled out or treated, the occurrence of a high number of breathing events overnight could skew the true PLMI value.

5.2 Muscle Activity Onset Detection

In both PSG and Medibyte recordings in this study, muscle activity onset detection was by visual inspection. An automated PLM detection algorithm is part of the EMG signal processing on the Medibyte®, but it did not identify any limb movements as PLMs in any of the sleep studies collected. Visual inspection has been the standard and has been considered to provide accurate detection of the onset of muscle activity in a surface EMG recording (Staude & Wolfe, 1999). However, accuracy is dependent on the skill and experience of the observer (Staude & Wolfe, 1999). This factor could have affected the reliability of the results of this
study. Inter-rater reliability for scoring the Medibyte® in the small subset of 5 recordings was not as strong (ICC = 0.78 (95% CI, 0.008 – 0.973), p < 0.05) as for intra-rater (0.97 (95% CI, 0.88 – 0.99) p < .001). This finding does suggest that differences in scoring skill were a source of error.

5.3 PLMI as an Outcome Measure

In PSG studies limb movements are reported as an index of number of PLMs per hour asleep. An overnight PLMI (sleep) ≥ 11 (Montplaisir, 1998) or an overnight PLMI (wake) ≥ 15 (Michaud, 2002) are considered supportive of a diagnosis of RLS, as is a SIT PLMI ≥11. While measurement of PLMs is the only objectively quantifiable measure of RLS status, there are problems associated with its use for this purpose. The inherent night-to-night variability of PLMs, and the fact that not all RLS patients experience PLMs (or necessarily experience them on a daily basis) affects the reproducibility of the measure and also the reliability of test retest measures (Michaud, 2006). Additionally, PLMs have been noted to occur in the elderly without any disruptions of sleep or other symptomatology, so are not necessarily specific to RLS (Kohnen et al., 2007, Park & Comella, 2007). In fact, it is documented that the prevalence of PLMs, without any pathological association or symptoms, normally increases with age (Hornyak, 2006). Thus any measurement of PLMI should always be considered in conjunction with severity of RLS symptoms.

5.4 RLS-Diagnostic Index (RLS-DI)

Diagnosis of RLS remains primarily a clinical judgment made by experienced medical specialists, usually based on subjective reports of patients. The specificity of the IRLSSG criteria is not perfect and cannot always rule out leg symptoms due to other conditions (Allen et al., 2005). The RLS-DI, a standardized diagnostic tool can be utilized by non-experts equally as well
as experts (Benes & Kohnen, 2009). The RLS-DI questionnaire, when compared with the “gold standard” of expert clinical interview demonstrated the ability to identify RLS patients from those with other conditions with a sensitivity of 93% and specificity of 98.9% and a total accuracy of 96.1% (Benes & Kohnen, 2009). The inclusion of the supportive features, especially the presence of PLMs and response to dopamine agonist, significantly increased the specificity of the tool for diagnosing RLS. Analysis of the essential criteria subscore alone (without the supportive criteria) only yielded a specificity of 81% for diagnosing RLS. Clearly, PLM measurement should be routine in suspected RLS to ensure a correct diagnosis. The work of this research supports the Medibyte® as a valid and reliable tool to measure PLMs. This tool would be a valuable adjunct to the RLS-DI for supporting an RLS diagnosis.

5.5 Minimal clinical difference

Key to using the Medibyte® to determine change in RLS status is knowledge of what is a minimal clinically significant change in PLMI. A review of a wide range of literature using PLMI as an objective measure, including both the World Association of Sleep Medicine (2006) and American Academy of Sleep Medicine (2007) guidelines, provides no definitive statement regarding what constitutes a clinically significant change in PLMI (Pennestri et al., 2006, Carrier et al., 2005). Coleman et al., (1982) initially suggested a level of 5 PLM/hour as a clinically significant value for discriminating healthy individuals from those with a PLM disorder. This level was increased, recognizing that individuals who do not have subjective complaints of RLS or sleep disturbance can experience PLMs (Hornyak et al., 2006). Most articles that state a PLMI cutoff value cite the work of Montplaisir et al (1998) recommending PLMI of 11 (higher value of two nights of study) as providing the best combination of sensitivity (81%) and specificity (81%) for the diagnosis of RLS. The AASM scoring manual (2007) recommends a PLMI of 15 as a specific cut off for RLS diagnosis based on the work of Michaud (2002b).
No standard of a minimal clinically significant difference for determining a change in RLS status is noted in any discussion of PLMI values. It is believed that this has not been addressed in the literature due to the difficulties with reliability in PLM measures. Most studies examining differences in RLS status have examined changes in the subjective scales, with some studies using PLMI as a secondary endpoint (Aukerman et al., 2006; Garcia-Borreguero et al., 2007; Montplaisir et al., 2006)

In studies that have used PLMI as a measure of severity, change scores have been reported as means and standard deviations (De Mello et al., 2004, Esteves, et al., 2008, Kume et al., 2009) and median values (Jama et al., 2009). Decreases in PLMI from overnight PSG reported by DeMello (2004) in a group of 13 spinal cord patients ranged from 35.11 ± 41.98 to 19.87 ± 25.46 with a 30 day course of L-Dopa and 18.53 ± 29.50 with a 45 day exercise program. In a group of 22 individuals with primary RLS, Esteves et al (2008) noted overnight PLMI decreases from 31.0 ± 18.4 to 24.2 ± 18.7 after one bout of intense physical exercise. After 72 sessions of aerobic exercise (approximately three times weekly for six months), overnight PLMI was down from 27.21 ± 4.73 to 14.79 ± 3.69 (Esteves et al., 2008). Kume et al (2009) examined PLM counts during a thirty-minute SIT with 18 hemodialysis patients. Prior to pergolide treatment mean SIT PLMI value was 41.9 ± 24.2. After four weeks of treatment, mean value was 11.3 ± 12.3 (p < 0.01), a mean difference of 30.6 (Kume et al., 2009). Based on these representative studies, overnight PLMI can change as little as 6.8 (one bout of exercise), to 16.58 (prolonged exercise), to as much as 30.6 (four weeks of medication), but the standard deviations are large.

Thus the question of how well the Medibyte can identify a minimal clinically significant change in PLMI cannot be established until it is known what value constitutes a minimal clinically significant change.
5.6 Suggested Immobility Test (SIT)

There has been much focused research attempting to streamline the process for obtaining a PLMI. The Suggested Immobilization Test (SIT) has been proposed as a method for measuring PLMs and RLS severity that does not involve the challenges of obtaining an overnight sleep study (Montplaisir et al., 1998).

There are several benefits to the SIT over PSG. As it does not involve measures of sleep, analysts do not have to discriminate leg movements on the basis of association with breathing events, the SIT is limited to one hour duration, it can be done during the peak of the reported symptoms for that particular patient and would not be limited to being done in a clinic or laboratory setting (Michaud, 2001; Michaud, 2002a; Montplaisir, 1998). Thus, it potentially eliminates some sources of error inherent in obtaining a PLMI.

Garcia-Borreguero, et al (2011) have explored a “multiple” SIT procedure to improve the reliability and reproducibility of PLM measures for this test. PLM counts and sensory discomfort scores were obtained during the SIT performed every two hours from noon to midnight (7 times). A SIT PLMI value was determined for controls (n=10), people with RLS that were on treatment (n = 19), and people with RLS that were untreated (n=19). It is not stated whether this was an average of all values in each person for each SIT or whether it was the highest value. The same sample of individuals with RLS was tested while on treatment with dopaminergic agents and 1-3 days after discontinuation of their medication. This test discriminated people with RLS from controls (PLMI 62.28 versus 6.06, \( p<0.001 \), no standard deviation given) and untreated (PLMI 62.28) from treated (PLMI 30.4 ±38.1, \( p < 0.01 \)) (Garcia-Borreguero et al., 2011).

The SIT increases the ease of objective testing for PLMs, which is much needed in the field of RLS assessment. A portable surface EMG monitoring device such as the Medibyte® would further increase the ease and utility of SIT procedures. Sources of error in the current
study that derived from complicated scoring procedures would not be an issue in scoring for PLMs in a SIT. Utilizing the Medibyte® during the SIT might logically increase the reliability of this device for obtaining a PLMI.

5.7 Portable Sleep Monitors versus Actigraphy for Measuring PLMs

Actigraphy has been more widely studied as a method for home measurement of PLMs than portable sleep monitors (Allen, 2007a; Sforza, Johannes, & Claudio, 2005; Van de Water, Holmes & Hurley, 2011; Gschliesser et al., 2009). All studies testing the PAM-RL®, an actigraphic device specifically for PLM measures, have found excellent reliability. Gschliesser et al., (2011) calculated \( r = 0.94 \) (\( P < 0.001 \)) when using the PAM-RL® bilaterally in ten participants, but mean difference in PLMI between the PAM-RL® and PSG was \( +26.6 \pm 20.5 \) PLMs/hour. In a larger group referred for a variety of sleep related disorders, including RLS, \( n=43 \), Sforza, Johannes, & Claudio, (2005) found a correlation of 0.89 (\( p < 0.0001 \)) between PLMI from PSG and PAM-RL®. These investigators found no significant difference in the “number of detected PLM activity” (p. 410) between the two methods but did acknowledge wide individual variance from – 34.7 to + 61.4.

Allen (2007a), who originally developed the PAM-RL®, recommended use of a sleep log and multiple night recordings to improve the accuracy of PLMI measurements with actigraphy. All authors (Allen, 2007a; Sforza, Johannes, & Claudio, 2005; Van de Water, Holmes & Hurley, 2011; Gschliesser et al., 2009) also recognized the issues with significant overestimation of PLMI by actigraphy if an individual has OSA or insomnia. None of these studies have examined ICC values for reliability. The only study to look at sensitivity and specificity was Sforza, Johannes, & Claudio (2005) who found that the PAM-RL® had a sensitivity of 0.88 and specificity of 0.76 for detecting patients with at least 10 PLM/h (95% CI: 0.72–0.90). The major deficiency with
actigraphy is that it does not measure PLMs as per the AASM (2007) criteria (i.e. EMG activity in association with respiratory measures) so this method lacks criterion validity (Portney & Watkins, 2009). Gschliesser et al (2009) acknowledge that for this reason, actigraphy cannot replace PSG.

Portable sleep monitors, which do not appear to have been as widely studied for reliability in obtaining a PLMI as limb movement monitors, are potentially able to obtain highly reliable PLMI values as shown by the current work. Additionally, the Medibyte® appears to demonstrate criterion/concurrent validity with the gold standard, PSG, for obtaining a PLMI.

5.8 Future Directions

There is still work to be done to establish this portable monitor as a valid tool for broad application in assessing PLMI. It should be evaluated for test retest reliability, and a minimal clinically significant difference established for detecting change in PLMI with the Medibyte®. The Medibyte® should be specifically tested versus PSG in an RLS population that does not also have possible sleep apnea to give a truer comparison of PLM counts between these two methods. Additional testing should be carried out in a truly random sample population including known RLS patients to accurately determine the reliability in differentiating between potentially confounding conditions (PLMD, Parkinson’s Disease, diabetic neuropathy, lumbar radiculopathy) and to determine sensitivity and specificity of the device for obtaining accurate cut off levels to support the diagnosis of RLS. The Medibyte® should be validated in special populations that have RLS secondarily to determine whether their primary condition (e.g. End-Stage Renal Disease undergoing hemodialysis, Chronic Obstructive Pulmonary Disease) has particular considerations that affect the reliability of the device and/or the its efficacy for PLM measurement (Winkelman, Chertow, & Lazarus, 1996; Kaplan, Inonu, Yilmaz & Ocal, 2008).
5.9 Conclusions and Recommendations

The results of this work investigating the validity and reliability of a portable monitor, the Braebon Medibyte®, against the gold standard, PSG, for obtaining a PLMI, demonstrate that the Medibyte® could be a valid tool to use for this measure. The good reliability of the device demonstrated by this research despite areas of concern, support the “real world” efficacy of this Medibyte® for obtaining a PLMI. Further, its portability and relative ease of use make it a preferred method over PSG. These features also enhance the accessibility of objective measurement of RLS status. If the Medibyte® is used in overnight studies with individuals with suspected RLS, OSA should be ruled out first and/or the individual should be under treatment for OSA in order to obtain the most reliable PLMI values. Used during a modified SIT procedure, a device such as this would, for the first time, make objective assessment of RLS available in an outpatient clinic setting and potentially significantly increase the use of PLMI by clinicians. In conjunction with the RLS Diagnostic Index, this monitor could expand the potential to adequately diagnose and treat RLS sufferers beyond the Sleep Medicine specialist and Sleep Laboratory resulting in larger numbers of RLS patients receiving proper assessment and treatment.
References


American Academy of Sleep Medicine. (2005). International classification of sleep disorders,


Collop, N. (2002). Scoring variability between polysomnography technologists in different sleep laboratories. Sleep Medicine, 3(1), 43-47.


Disorders, 17(1), 112-115.


*Psychological Bulletin.* 86(2), 420-428.


sleep (PLMS) and wakefulness (PLMW) developed in collaboration with a task force from the International Restless Legs Syndrome Study Group (IRLSSG). Sleep Medicine, 7(2), 175-183.
7.1 Definitions of Breathing Events During Sleep

HYPOPNEA

Clinical Definition: Several clinical definitions of hypopnea are in clinical use and there is no clear consensus. A Centers for Medicare and Medicaid Services (CMS)-approved definition of hypopnea is an abnormal respiratory event with at least a 30% reduction in thoracoabdominal movement or airflow as compared to baseline lasting at least 10 seconds, and with >4% oxygen desaturation. Obstruction is often inferred from thoracoabdominal paradox, the shape of the flow signal, or when snoring intensity increases during the event.

Research Definition*: A clear amplitude reduction of a validated measure of breathing during sleep (but less than a 50% reduction from baseline) that is associated with an oxygen desaturation of >3% or an arousal. Only an esophageal balloon can demonstrate the hypopnea to be obstructive vs. central.

OBSTRUCTIVE APNEA

Clinical Definition: Apnea is defined as a cessation of airflow for at least 10 seconds. The event is obstructive if during apnea there is effort to breathe.

Research Definition*: A clear decrease (>50%) from baseline in the amplitude of a valid measure of breathing during sleep lasting at least 10 seconds (note, little difference made between obstructive apnea or hypopnea)

CENTRAL APNEA

Clinical Definition: Apnea is defined as a cessation of airflow for at least 10 seconds. The event is central if during apnea there is no effort to breathe.

Research Definition*: Same as above, but an esophageal balloon must verify lack of effort.

Clinical Definition: Apnea is defined as a cessation of airflow for at least 10 seconds. The event is mixed if the apnea begins as a central apnea, but towards the end there is effort to breathe without airflow.

RESPIRATORY-EFFORT RELATED AROUSAL (RERA)

Clinical Definition: Not agreed upon.

Research Definition*: Sequence of breaths with increasing respiratory effort leading to an arousal from sleep, as shown by progressively more negative esophageal pressure for at least 10 seconds preceding an arousal with resumption of more normal pressures.

7.2 **International Restless Legs Syndrome Study Group Severity Scale**

**International Restless Legs Syndrome Study Group Rating Scale (IRLS)**

(Investigator Version 2.2)

Have the patient rate his/her symptoms for the following ten questions. The patient and not the examiner should make the ratings, but the examiner should be available to clarify any misunderstandings the patient may have about the questions. The examiner should mark the patient's answers on the form.

In the past week…

(1) Overall, how would you rate the RLS discomfort in your legs or arms?

4 □ Very severe
3 □ Severe
2 □ Moderate
1 □ Mild
0 □ None

In the past week…

(2) Overall, how would you rate the need to move around because of your RLS symptoms?

4 □ Very severe
3 □ Severe
2 □ Moderate
1 □ Mild
0 □ None

In the past week…

(3) Overall, how much relief of your RLS arm or leg discomfort did you get from moving around?

4 □ No relief
3 □ Mild relief
2 □ Moderate relief
1 □ Either complete or almost complete relief
0 □ No RLS symptoms to be relieved
In the past week…
(4) How severe was your sleep disturbance due to your RLS symptoms?

4 □ Very severe
3 □ Severe
2 □ Moderate
1 □ Mild
0 □ None

In the past week…
(5) How severe was your tiredness or sleepiness during the day due to your RLS symptoms?

4 □ Very severe
3 □ Severe
2 □ Moderate
1 □ Mild
0 □ None

In the past week…
(6) How severe was your RLS as a whole?

4 □ Very severe
3 □ Severe
2 □ Moderate
1 □ Mild
0 □ None

In the past week…
(7) How often did you get RLS symptoms?

4 □ Very often (This means 6 to 7 days a week)
3 □ Often (This means 4 to 5 days a week)
2 □ Sometimes (This means 2 to 3 days a week)
1 □ Occasionally (This means 1 day a week)
0 □ Never
In the past week…
(8) When you had RLS symptoms, how severe were they on average?

4 □ Very severe (This means 8 hours or more per 24-hour day)
3 □ Severe (This means 3 to 8 hours per 24-hour day)
2 □ Moderate (This means 1 to 3 hours per 24-hour day)
1 □ Mild (This means less than 1 hour per 24-hour day)
0 □ None

In the past week…
(9) Overall, how severe was the impact of your RLS symptoms on your ability to carry out your daily affairs, for example carrying out a satisfactory family, home, social, school or work life?

4 □ Very severe
3 □ Severe
2 □ Moderate
1 □ Mild
0 □ None

In the past week…
(10) How severe was your mood disturbance due to your RLS symptoms - for example angry, depressed, sad, anxious or irritable?

4 □ Very severe
3 □ Severe
2 □ Moderate
1 □ Mild
0 □ None
7.3 Scoring of the IRLSSG Severity Scale

International Restless Legs Syndrome Study Group Rating Scale (IRLS)

SCALING AND SCORING OF THE
‘International Restless Legs Syndrome Study Group Rating Scale’ (IRLS)

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69003 Lyon
France
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Contact:
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The International Restless Legs Syndrome Study Group (IRLSG)

Represented by
Dr Arthur Walters
E-mail: ArtUMDNJ@aol.com

Dr Richard Allen
E-mail: RichardJU-IU@aol.com

Version 1: January 2008
The IRLS is composed of 10 items. It gives a global score for all 10 items that is most commonly used as an overall severity score. 9 of the 10 items investigate two dimensions of the RLS severity.

**DESCRIPTION OF THE QUESTIONNAIRE:**

<table>
<thead>
<tr>
<th>Dimensions</th>
<th>Number of Items</th>
<th>Cluster of Items</th>
<th>Item Reversion</th>
<th>Direction of Dimensions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symptoms</td>
<td>6</td>
<td>1, 2, 4, 6, 7</td>
<td>No</td>
<td>Higher score = Higher severity</td>
</tr>
<tr>
<td>Symptoms impact</td>
<td>3</td>
<td>5, 9 and 10</td>
<td>No</td>
<td>Higher score = Higher impact</td>
</tr>
</tbody>
</table>

Item 3 is part of the diagnostic criteria and does not belong to any of the two dimensions. It is used for the total score for overall RLS severity.

**SCORING OF DIMENSIONS:**

<table>
<thead>
<tr>
<th>Item scaling</th>
<th>5-point Likert scale from 0 “None” to 4 “very severe”</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weighting of Items</td>
<td>No</td>
</tr>
<tr>
<td>Extension of the Scoring Scale</td>
<td>Symptom severity subscale: 0-24 Impact on daily living subscale: 0-12 Global score: 0-40</td>
</tr>
<tr>
<td>Scoring Procedure</td>
<td>The score of each subscale is calculated by summing the scores of all items of the subscale The global score is obtained by summing all the 10 items scores</td>
</tr>
<tr>
<td>Interpretation and Analysis of missing data*</td>
<td>All 10 items should be completed to calculate the global score For the symptoms subscale, all six items should be completed to calculate the subscale score For the symptoms impact subscale, all three items should be completed to calculate the subscale score</td>
</tr>
<tr>
<td>Interpretation and Analysis of ‘non-concerned’ answers</td>
<td>Not applicable for this questionnaire. Subjects should not be administered the scale unless they meet the 4 IRLSSG criteria for Restless Legs Syndrome</td>
</tr>
</tbody>
</table>

* This scale should be read to the patient by a trained staff member with the patient looking at the questions and providing a verbal answer. The staff member and not the patient records the patient’s answer. In this situation there should be no missing items. If missing items occur the staff member failed to properly administer the scale and the results should probably not be accepted. Pro-rating for missing answers should not be needed for this scale.

Version 1: January 2008
REFERENCE(S):

The International Restless Legs Syndrome Study Group. Validation of the International Restless Legs Syndrome Study Group rating scale for restless legs syndrome. Sleep medicine. 2003;4:121-132


### 7.4 RLS-DI (Diagnostic Index)

#### Restless Legs Syndrome Diagnostic Index (RLS-DI)

**Definition:** The Restless Legs Syndrome (RLS) is defined as an urge to move focused on the legs (and arms in some patients). This urge to move often but not always is associated with other unpleasant abnormal sensations occurring without any apparent sensory stimulation. The urge to move and any accompanying unpleasant sensations must be engendered by rest, relieved by movement and worse in the evening or night with some relief in the morning. The physician should interview the patient about the occurrence of complaints typical or supportive for RLS or complaints frequently associated with RLS.

The time period of assessments for items 1 to 6 refers to the past 7 days. For evaluation of items 8 to 10, data from medical history can be used except that an actual sleep lab or neurological examination is indicated due to specific symptoms of the patient (e.g. back pain).

<table>
<thead>
<tr>
<th>Essential criteria</th>
<th>Occurs regularly (on ≥ 5 of 7 days)</th>
<th>Occurs occasionally (on 1 to 4 of 7 days)</th>
<th>Not applicable / not present</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Do you feel an urge to move your legs (arms)?</td>
<td>2</td>
<td>1</td>
<td>-4</td>
</tr>
<tr>
<td>2. When feeling an urge to move, do you experience unpleasant sensations in legs (arms) such as itching, stabbing, pulling, pain?</td>
<td>2</td>
<td>1</td>
<td>-4</td>
</tr>
<tr>
<td>3. Do your urge to move / unpleasant sensations begin or worsen when you are at rest (lying, sitting) or when you are inactive?</td>
<td>2</td>
<td>1</td>
<td>-4</td>
</tr>
<tr>
<td>4. Is there relief of urge to move / unpleasant sensations, partially or complete, by movement (e.g., walking or stretching)?</td>
<td>2</td>
<td>1</td>
<td>-4</td>
</tr>
<tr>
<td>5. Are urge to move / unpleasant sensations worse in the evening or at night than during the day? (That means, complaints are worse at night than during the day or occur only in the evening or at night). In severe RLS, this criterion must have been previously present.</td>
<td>2</td>
<td>1</td>
<td>-1</td>
</tr>
</tbody>
</table>

The following items are to be assessed by the physician interviewing the patient as well as in consideration of medical records and clinical findings. **Please evaluate at first item 6, 7 and 8.** In the event the data were not (yet) collected, please tick the column “Not assessable / not done”.

<table>
<thead>
<tr>
<th>Associated and supportive criteria</th>
<th>Definite</th>
<th>Uncertain</th>
<th>No</th>
<th>Not assessable / not done</th>
</tr>
</thead>
<tbody>
<tr>
<td>6. Does the patient suffer from sleep disturbance? (That means: prolonged time to fall asleep, sleep interrupted, sleep duration shortened during the past 7 days)</td>
<td>2</td>
<td>1</td>
<td>-1</td>
<td></td>
</tr>
<tr>
<td>7. Does a first-degree relative (parents, brothers and sisters, children) suffer from urge to move / unpleasant sensations (item 1-5)</td>
<td>2</td>
<td>1</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>8. Did urge to move / unpleasant sensations ever improved with dopaminergic therapy? (Any previous and current treatment with L-dopa or dopaminergic agonists)</td>
<td>2</td>
<td>1</td>
<td>-4</td>
<td></td>
</tr>
<tr>
<td>9. Objective findings of PLM in PSG / actimetry and/or SIT (e.g., PLM/h &gt;15 and/or PLMS Arousal Index &gt;5/h and/or PLMW)</td>
<td>2</td>
<td>1</td>
<td>-2</td>
<td></td>
</tr>
<tr>
<td>10. Can urge to move / unpleasant sensations be sufficiently explained by other medical factors/concomitant diseases? Note: Please do not consider medical and pharmacological conditions which can cause a “secondary” RLS. Please specify the cause of secondary RLS, if applicable.</td>
<td>-4</td>
<td>-1</td>
<td>2</td>
<td>0</td>
</tr>
</tbody>
</table>

**Diagnostic process:**
- Stop the interview if score of item 1 = -4: no RLS
- Stop the interview if the sum-score of items 1 to 5 is <4: no RLS
- Stop the interview if the sum-score of items 1 to 8 is ≥11: RLS
7.5 Study 1 Letter of Information and Consent

Letter of Information & Consent Form

Course Project for Data Acquisition and Instrumentation

Comparison of the Braebon Medibyte home sleep monitor auxiliary EMG channel recording of repeated tibialis anterior contraction with standard surface EMG recording.

Dear Participant,

I would like to invite you to participate in a research study that is part of my graduate course requirement in Data Acquisition and Instrumentation. I will review this letter with you and describe the procedures before asking for you to sign this consent form. Please feel free to ask questions at any time. This study has been granted clearance according to the recommended principles of Canadian ethics guidelines, and Queen's policies.

Purpose and Aims of the Study:
The Data Acquisition and Instrumentation course is run by Professors Linda McLean and Joan Stevenson. The purpose of this study is to validate the use of the Medibyte home sleep monitor for detection of the typical lower leg movements that occur in Restless Legs Syndrome. The Medibyte does not detect muscle activity with the same precision as standard electromyography (EMG). It is hoped to be able to show that, despite this, the Medibyte will detect the typical muscle activity in the lower leg well enough, as compared to standard surface EMG, to be valid for use in recording a periodic limb movement index. This would allow the unit to be used for home measurement of the periodic limb movements that help to diagnose Restless Legs Syndrome.

Exclusion Criteria:
To minimize risks of injury during this study, I will exclude you if you have any current dysfunction in your lower limb i.e. sports injury, arthritis, neurological condition (stroke, cerebral palsy), any ankle or foot pain that affects movement.

Preparation for Data Collection
If you accept this invitation to participate in this study, you will be asked to warm-up before we conduct the study by walking up and down the hallway outside the Motor Performance Lab twice. Then two self-adhesive surface electrodes will be placed on your skin over the front of each lower leg. Once the instrumentation is in place, you will be asked to perform a calibration procedure of 2 or 3 ankle movements. This whole process will take about 10-15 minutes.

Data Collection Procedures
Once we are ready, I will ask you to perform 2 or 3 practice trials to verify my instrumentation and your understanding of the procedure. Then I will ask you to repeat the ankle movements multiple times at a specific speed and interval. Your data will be saved in a computer program under a subject code, not your name. The test procedure is expected to take about 30 minutes.

Risks of Participation
There are no physiological risks associated with surface EMG recordings or wearing of the Medibyte device. There may be a risk of the electrode preparation and/or the tape abrading the skin and causing skin irritation for some individuals but this irritation normally disappears shortly after the tape is removed. If you feel skin irritation, extended muscular soreness or pain after completion of your
participation, please contact me or Dr McLean and go to a medical centre for assistance or contact your preferred health care professional.

**Benefits of Participation:**

The benefits of this study are minimal for you. You will have a chance gain some experience with scientific testing and learn more about EMG recording and periodic limb movements in Restless Legs Syndrome. Your participation will potentially assist in validating the Medibyte device for the home measurement of PLMs to aid in the diagnosis of Restless Legs Syndrome. This would provide a convenient, relatively inexpensive and more easily accessible method than the current standard of polysomnogram, which requires an overnight stay in a sleep lab.

**Confidentiality:**

Your confidentiality and your anonymity will be protected as much as possible. As this is a course project, others in the class may be aware that you have volunteered for this study. However, I will not reveal your identity. You will be identified by a code number on all data files with your name stored separately from the data. All data records in computer files will be locked and discarded at the end of the course or after publication. Only summary data and/or code numbers will be used during the presentation/publication.

I would like to ask at least one participant to permit me to take photographs during the task for use in future presentations and/or publications. This photographs are not needed for data analyses, merely to demonstrate the protocol used in the study. If you are willing to have your photograph taken, I will ask you to sign the section at the bottom of this form granting your permission.

**Voluntary Nature of the Study:**

Your participation in this study is completely voluntary and is not a required as part of this course. You may withdraw from this study at any time without penalty or coercion. Your data will be removed if you wish it withdrawn. A decision to withdraw will have no effect on your academic standing.

**Contacts:**

If at any time you have further questions, problems or adverse events, you can contact:

Mary Jane O’Donovan PT (MSc Candidate)  odonovan.m.j@queensu.ca   (613) 533-6103
Dr. Linda McLean (Professor of my course)  mcleanl@queensu.ca   (613) 533-6101
Dr. Joan Stevenson (Research Ethics Board, Chair)  chair.GREB@queensu.ca   (613) 533-6801

**Liability:**

By signing the consent form, you do NOT waive your legal rights nor release the investigator(s) from their legal and professional responsibilities.

**Subject Statement and Signature:**

As a volunteer participant, I have read and understand the consent form for this study. The purposes, procedures and technical language have been explained to me. I have been given sufficient time to consider the above information and withdraw if I choose to do so. I have had the opportunity to ask questions which have been answered to my satisfaction. I understand that I can withdraw at any time. I understand that my participation is in confidence and that my data will be identified by code name only to the class. I am voluntarily signing this consent form below. I will receive a copy of this consent form for future reference.
By signing this consent form, I am indicating that I agree to participate in this study.

Signature of Participant ____________________________ Date ____________________________

Consent for Photographs:

By signing below, I am indicating my willingness to be photographed for presentations or publications. I realize my face will be blocked from view in these images.

Signature of Participant ____________________________ Date ____________________________

By signing this consent form, I confirm that I have carefully explained the nature of the above research study to the subject. I certify that, to the best of my knowledge, the subject understands clearly the nature of the study and the demands, benefits, and risks involved to participants in this study.

Signature of Witness ____________________________ Date ____________________________
7.6 Study 1 Ethics Approval

MEMO

To: Mary Jane O’Donovan
Graduate Student in RHBS-837

From: Joan Stevenson
School of Kinesiology and Health Studies

Re: Electromyography (RHBS 837) Research Project: “Comparison of the Braebon Medbyte home sleeper monitor ancillary EMG channel recording of repeated tibialis anterior contraction with a standard surface EMG recording”

Date: February 6, 2011

By this letter, I am providing ethics clearance to proceed with the above study for your project in the Data Acquisition and Instrumentation course. This approval is for coursework only and if you wish to continue this research project beyond the 2011 winter academic term, it must receive approval from either the General Research Ethics Board or the Health Sciences Research Ethics Board.

If any adverse events occur in your study, you must contact either Linda McLean or myself within 24 hours. We will assist you with immediate solutions and report this adverse event(s) through Joan Stevenson to the General Research Ethics Board on the appropriate form. An adverse event includes, but is not limited to, a complaint, a change or unexpected event that alters the level of risk for the researcher or participants or situation that requires a substantial change in approach to a participant(s).

If you make any changes to your research study, please document it in an email to Linda Mclean and myself and submit a changed Consent Form (if applicable) as we are responsible for approving all changes. I wish you success in your research project.

Yours sincerely,

Joan M. Stevenson, PhD
Course Instructor

Cc: Dr. Linda McLean, RHBS
7.7 Study 2 Letter of Information and Consent

Sleep Disorders Clinic
Sleep Laboratory
Kingston General Hospital

Mailing Address
Room 20-103, Richardson House
Queen’s University
102 Stuart Street
Kingston, Ontario K7L 2V6

SUBJECT INFORMATION / CONSENT FORM

TITLE OF PROJECT: Pilot evaluation of a portable home monitoring device (MediByte) for screening of obstructive sleep apnea: Comparison with laboratory polysomnography.

Principal Investigator: Dr. Helen S. Driver, (613) 548-6052.
Study Coordinator: Effie J. Pereira, (613) 549-6666 ext. 3214.

Background information: You are being invited to participate in a research study directed by Dr. Helen Driver, Ph.D. and Dr. Michael Fitzpatrick, M.D. to evaluate a portable home screening device in the diagnosis of obstructive sleep apnea (OSA) when compared to the gold-standard in-laboratory sleep recording – polysomnography with the attendance of a sleep technologist. The research assistant will read through this consent form with you and describe procedures in detail and answer any questions you may have. This pilot study has been reviewed for ethical compliance by the Queen’s University Health Sciences and Affiliated Teaching Hospitals Research Ethics Board.

DETAILS OF THE STUDY: The purpose of this study is to compare the accuracy of a sleep screening device (MediByte®, Braebon Medical Corporation) with routine standard laboratory recording and overnight Home Sleep Testing (HST). You will be considered for the study if you have been referred to the sleep disorders laboratory by your physician and are at the sleep laboratory for a routine diagnostic overnight study.

In addition to the routine electrodes, belts and sensors for your sleep study, you will be asked to wear a few duplicate electrodes and belts. Measures recorded in duplicate will be:
- Respiratory effort belts - 2 around your chest and 2 around your abdomen
- 2 snore sensors (one on your neck and another on your forehead)
- 2 finger sensors for measure oxygen levels (oximetry)
- 2 electrodes on each leg for recording leg movements
- 3 electrodes for ECG recording in addition to the routine 2 electrodes
- An additional electrode on your forehead and one at the front of your head
- To monitor airflow via a nasal cannula pressure transducer, you will only need to wear one cannula and the signal will be split to run through two pressure transducers.

Possible risks from participating in this project: There are no risks to using the equipment, aside from slightly more discomfort from additional sensors. If you find that you are uncomfortable with the additional sensors, you may remove them at any time.

Possible benefits from participating in this project: There are no direct benefits to you for participating in this study, aside from having duplicate data on some measures. The potential to use the device as a home portable monitoring unit could possibly reduce wait times for patients and allow access to some patients who need studies in the home environment.

Confidentiality and Privacy: All information obtained during the course of this study is strictly confidential and your anonymity will be protected at all times. You will be identified by a code. Data will be stored in a locked office and will be available only to principal investigators, research assistant, or Braebon Medical Corporation. You will not be identified in any publication or reports.

Your participation in this study is voluntary. You may withdraw from this study at any time and your withdrawal will not affect your future medical care with your physician or at this hospital.

Contact persons for this study: You may contact Dr. H. Driver (Principal Investigator) at (613) 548-6052, or Dr. J. McCans (Head, Department of Medicine) at (613) 533-6327, or Dr. A. Clark (Chair, Research Ethics Board) at (613) 533-6081 with any questions or concerns regarding this study.
CONSENT FORM

Statement & Signature Section: I have read and understand the consent form for this study. I have had the purposes, procedures and technical language of this study explained to me. I have been given sufficient time to consider the above information and to seek advice if I chose to do so. I have had the opportunity to ask questions which have been answered to my satisfaction. I am voluntarily signing this form. I will receive a copy of this consent form for my information.

By signing this consent form, I am indicating that I agree to participate in this study.

______________________________________________  ____________________________
Signature of Patient                               Date

______________________________________________  ____________________________
Signature of Witness                               Date

Statement of the Investigator: I, or one of my colleagues, have carefully explained to the subject the nature of the above research study. I certify that, to the best of my knowledge, the subject understands clearly the nature of the study and demands, benefits, and risks involved to participants in this study.

______________________________________________  ____________________________
Signature of Principal Investigator                Date

Principal Investigator: Dr. Helen Driver, (613) 548-6052.
Study Coordinator: Effie J. Pereira, (613) 549-6666 ext. 3214.
May 27, 2010

Dr. Helen Driver  
Department of Medicine  
Sleep Disorders Laboratory, Kidd 6  
Kingston General Hospital

Re: “Pilot evaluation of a portable home monitoring device (MediByte) for screening of obstructive sleep apnea: Comparison with laboratory polysomnography” DMED-1003-07

Dear Dr. Driver,

I am writing to acknowledge receipt of your request for an amendment to the study. I have reviewed this request to recruit 50 more patients to conduct a new analysis and hereby give my approval. This amendment will be reported to the Health Sciences Research Ethics Board. An approval/renewal sheet is appended for your records.

Yours sincerely,

Albert Clark, Ph.D.  
Chair  
Research Ethics Board

AFC/kr
QUEEN'S UNIVERSITY HEALTH SCIENCES AND AFFILIATED TEACHING HOSPITALS
ANNUAL RENEWAL

Queen's University, in accordance with the “Tri-Council Policy Statement, 1998” prepared by the Medical Research Council, Natural Sciences and Engineering Research Council of Canada and Social Sciences and Humanities Research Council of Canada requires that research projects involving human subjects be reviewed annually to determine their acceptability on ethical grounds.

A Research Ethics Board composed of:

Dr. A.F. Clark
Emeritus Professor, Department of Biochemistry, Faculty of Health Sciences, Queen's University (Chair)

Dr. H. Abdollah
Professor, Department of Medicine, Queen's University

Rev. T. Deline
Community Member

Dr. M. Evans
Community Member

Dr. S. Irving
Psychologist, Providence Care, St. Mary's of the Lake Hospital Site

Dr. L. Keeping-Burke
Assistant Professor, School of Nursing, Queen's University

Dr. J. Low
Emeritus Professor, Department of Obstetrics and Gynaecology, Queen's University and Kingston General Hospital

Ms. D. Morales
Community Member

Dr. W. Racz
Emeritus Professor, Department of Pharmacology & Toxicology, Queen's University

Dr. B. Simchison
Assistant Professor, Department of Anaesthesiology, Queen's University

Dr. A.N. Singh
WHO Professor in Psychosomatic Medicine and Psychopharmacology
Professor of Psychiatry and Pharmacology
Chair and Head, Division of Psychopharmacology, Queen's University
Director & Chief of Psychiatry, Academic Unit, Quinte Health Care, Belleville General Hospital

Dr. E. Tsai
Associate Professor, Department of Paediatrics and Office of Bioethics, Queen's University

Rev. J. Warren
Community Member

Ms. K. Weisbaum
L.L.B. and Adjunct Instructor, Department of Family Medicine (Bioethics)

Dr. S. Wood
Director, Office of Research Services (Ex Officio)

has reviewed the request for renewal of Research Ethics Board approval for the project “Pilot evaluation of a portable home monitoring device (MediByte) for screening of obstructive sleep apnea: Comparison with laboratory polysomnography” as proposed by Dr. Helen Driver of the Department of Medicine, at Queen’s University. The approval is renewed for one year, effective May 11, 2010. If there are any further amendments or changes to the protocol affecting the subjects in this study, it is the responsibility of the principal investigator to notify the Research Ethics Board. Any unexpected serious adverse event occurring locally must be reported within 2 working days or earlier if required by the study sponsor. All other adverse events must be reported within 15 days after becoming aware of the information.

Chair, Research Ethics Board

Date

ORIGINAL TO INVESTIGATOR - COPY TO DEPARTMENT HEAD - COPY TO HOSPITAL(S) - FILE COPY
Renewal 1 [ ] Renewal 2 [x] Extension [x]
REB# DMED-1003-07
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Dr. M. Evans  Community Member

Dr. S. Horgan  Manager, Program Evaluation & Health Services Development, Geriatric Psychiatry Service, Providence Care, Mental Health Services

Dr. L. Keeping-Burke  Assistant Professor, Department of Psychiatry

Ms. D. Morales  Assistant Professor, School of Nursing, Queen's University

Dr. W. Racz  Emeritus Professor, Department of Pharmacology & Toxicology, Queen's University

Dr. B. Simchison  Department of Anaesthesiology, Queen's University

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Chair, Research Ethics Board  Date

ORIGINAL TO INVESTIGATOR - COPY TO DEPARTMENT HEAD - COPY TO HOSPITAL(S) - FILE COPY - BINDER COPY

REB# DMED-1003-07
QUEEN'S UNIVERSITY HEALTH SCIENCES AND AFFILIATED TEACHING HOSPITALS ANNUAL RENEWAL

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A Research Ethics Board composed of:

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Dr. H. Abdollah, Professor, Department of Medicine, Queen's University
Dr. R. Brison, Professor, Department of Emergency Medicine, Queen's University
Dr. M. Evans, Community Member
Dr. S. Horgan, Manager, Program Evaluation & Health Services Development, Geriatric Psychiatry Service, Providence Care, Mental Health Services Assistant Professor, Department of Psychiatry
Ms. J. Hudacin, Community Member
Dr. B. S. Kisilevsky, Professor, School of Nursing, Departments of Psychology and Obstetrics & Gynaecology, Queen's University
Ms. D. Morales, Community Member
Ms. P. Newman, Pharmacist, Clinical Care Specialist and Clinical Lead, Quality and Safety, Pharmacy Services, Kingston General Hospital
Dr. W. Racz, Emeritus Professor, Department of Pharmacology & Toxicology, Queen's University
Ms. S. Rohland, Privacy Officer, ICES-Queen's Health Services Research Facility, Research Associate, Division of Cancer Care and Epidemiology, Queen's Cancer Research Institute
Dr. B. Simchison, Assistant Professor, Department of Anaesthesiology, Queen's University
Dr. A.N. Singh, WHO Professor in Psychosomatic Medicine and Psychopharmacology Professor of Psychiatry and Pharmacology Chair and Head, Division of Psychopharmacology, Queen's University Director & Chief of Psychiatry, Academic Unit, Quinte Health Care, Belleville General Hospital
Dr. E. Tsai, Associate Professor, Department of Paediatrics and Office of Bioethics, Queen's University

has reviewed the request for renewal of Research Ethics Board approval for the project "Pilot Evaluation of a Portable Home Monitoring Device (MediByte) for Screening of Obstructive Sleep Apnea: Comparison With Laboratory Polysomnography" as proposed by Dr. H. Driver of the Department of Medicine, at Queen's University. The approval is renewed for one year, effective January 11, 2012. If there are any further amendments or changes to the protocol affecting the participants in this study, it is the responsibility of the principal investigator to notify the Research Ethics Board. Any unexpected serious adverse event occurring locally must be reported within 2 working days or earlier if required by the study sponsor. All other adverse events must be reported within 15 days after becoming aware of the information.

Albert J. Clark, Chair, Research Ethics Board

Renewal 1[ ] Renewal 2 [ ] Extension [x ] Code# DMED-1003-07 Romeo file# 6004601

Date: December 19, 2011

126